Original article

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Management and monitoring of patients treated with zonisamide: the OZONE study

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ABSTRACT – *Aim*. To characterise patients treated with zonisamide in everyday practice and describe the effectiveness and tolerability of treatment. *Methods*. This was an observational, longitudinal, naturalistic study, conducted by neurologists in France. Patients who had started zonisamide treatment at least three months prior to inclusion were eligible. Data were collected at routine consultations at inclusion (Visit 1) and three to six months later (Visit 2). At Visit 1, investigators documented epilepsy-related variables based on patient records before initiation of zonisamide and at inclusion. At Visit 2, the investigators re-evaluated seizure activity and rated effectiveness. Adverse events were also documented. *Results*. A total of 428 patients were included in the study based on evaluation by 132 neurologists. Zonisamide was initiated at a daily dose of 50 mg and 25 mg in 61% and 31.8% of patients, respectively. The median maintenance dose was 300 mg/day. Prior to initiation of zonisamide, the mean seizure frequency was 16.0 seizures/month. This was reduced to 8.7 seizures/month at Visit 1 and to 7.1 seizures/month at Visit 2. The response rate and proportion of seizure-free patients was 61.9 and 31.1% at Visit 1 and 65.9 and 25.6% at Visit 2, respectively. The frequency of seizures at Visit 2 decreased significantly ($p<0.05$) for all seizure type subgroups, except for simple partial seizures. Responder rates were >60% for all analysed subgroups. The proportion of seizure-free patients was significantly higher in patients receiving bitherapy, compared to the others ($p=0.007$). The most frequently reported adverse event was somnolence (5.1%); three serious adverse events were reported. *Conclusion*. In everyday practice, zonisamide is principally used in association with other antiepileptic drugs for the treatment of focal epilepsy in adults. It is effective in improving seizure control and quality of life, and is generally well-tolerated.

Key words: zonisamide, treatment, epilepsy, management, monitoring

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In order to meet the challenge of pharmacoresistant epilepsy, novel antiepileptic drugs (AEDs) continue to be developed and introduced into clinical practice. For regulatory purposes, randomised controlled trials (RCTs) are considered as the "gold standard" for determining efficacy and safety of drugs (Arzimanoglou *et al*., 2010). However, for many reasons, RCTs do not reflect the real efficacy and tolerability of these drugs. Firstly, treatment regimens are used that do not necessarily match how AEDs are used in everyday practice. Indeed, titration is usually too fast and imposed, the dosages that are to be reached are often too high, and the possibilities for dose-adjustment of the drugs and other co-medication are very limited. Secondly, patients in RCTs have been highly selected and the majority have refractory epilepsy (Arzimanoglou *et al*., 2010).

Epilepsy is a chronic and complex disease that requires long-term treatment, which needs to be adapted on an individual patient basis in order to ensure that each patient receives an AED at an effective and tolerated dose. Although drugs have already been approved by regulatory bodies on the basis of RCTs, observational studies that include heterogeneous population, flexible dosing regimens, and individualised treatment trajectories are necessary to complete the data from RCTs.

Zonisamide (zonegran), a benzisoxazole derivative, has potentially multiple modes of action, including blockade of voltage-dependant sodium channels and T-type calcium channels, as well as facilitation of inhibitory GABAergic neurotransmission (Baulac, 2006). Four pivotal randomised double-blind clinical trials, performed between 1993 and 2005, have demonstrated its efficacy and tolerability, compared to placebo, in a dose-dependent fashion (Schmidt *et al*., 1993; Faught *et al*., 2001; Sackellares *et al*., 2004; Brodie *et al*., 2005). On this basis, zonisamide was approved in Europe in 2005 for the adjunctive treatment of epilepsy in adult patients with focal seizures with or without secondary generalisation. To date, the use of zonisamide in association with the new AEDs, that now dominate everyday clinical practice, as well as the consequence of long-term use, is not well documented. Accordingly, we performed a naturalistic, non-interventional study of the use of zonisamide in everyday clinical practice in France, for the adjunctive treatment of focal epilepsy over a 12-month observation period.

The primary objective of the study was to characterise epilepsy patients treated with zonisamide in everyday practice. Secondary objectives were to describe the effectiveness of treatment with respect to seizure frequency and quality of life (QoL), in order to assess tolerability and document treatment modalities with respect to dose regimen and associated AED treatments.

Methods

Study design

This was an observational, longitudinal, naturalistic study conducted by hospitals or community neurologists in France, between May 2008 and March 2010. The total anticipated duration of the study was 12 months.

Selection of centre and patients

Participating neurologists were selected at random from an exhaustive list of all neurologists practicing in France (around 2,250), provided by CEGEDIM (Boulogne, France). Fifteen hundred randomly selected physicians from this list were contacted by mail and invited to participate in the study.

Patients included

Patients were included in the study by all participating neurologists who were expected to enrol the next one or two patients, consecutively, seen in consultation. The inclusion period lasted for three months. All adult patients requiring adjunctive antiepileptic treatment, and for whom treatment with zonisamide had been initiated at least three months before inclusion, were eligible for participation in the study. Patients aged less than 18 years, those with generalised epilepsy, or those treated with zonisamide as monotherapy were excluded.

Study procedures and data collection

All data were collected by medical interview or from patients' medical records at routine follow-up visits.

Data were collected at two routine consultations; one at the time of inclusion (Visit 1, at least three months after initiation of zonisamide) and a second follow-up visit three to six months later (Visit 2). At Visit 1, the neurologist verified the inclusion criteria and obtained signed consent from participating patients. Data on sociodemographics and medical history was obtained and recorded in the case report form (CRF). In addition, investigators provided retrospective data, obtained from the patient records, on epilepsy-related variables (duration and type of seizures, frequency of seizures, and AED treatment) and the zonisamide treatment regimen at the time when zonisamide was initiated. The reasons for choosing zonisamide were provided. Any adverse events, possibly or probably related to zonisamide treatment that had occurred during the intervening period, were documented. At Visit 1, the investigator also provided information on current seizure frequency and any modifications to the zonisamide treatment regimen.

At Visit 2, the investigator re-evaluated seizure frequency and rated the progression of autonomy, cognitive symptoms, and behavioural symptoms on a 5-item checklist (absent, improved, stable, worsened, or not evaluated) as well as the effectiveness of zonisamide on these symptoms using a 5-item Likert scale (very effective, effective, not very effective, ineffective, undetermined). Data were provided regarding any changes to the zonisamide treatment regimen, adverse events, reasons for any treatment discontinuation, or any anticipated changes in treatment. In addition, at both study visits, patients were asked to complete a visual analogue scale (VAS) in order to evaluate evolution of seizures and quality of life.

Statistical analysis

The number of patients to be included was determined *a priori* by power calculations. In order to estimate an anticipated frequency of the principal study variables with a precision of 2.5% and a bilateral α risk of 0.05, it was necessary to evaluate 553 patients. Assuming that 90% of included patients could be evaluated, it would be necessary to include 614 patients in the study. Since participants were asked to include one or two patients in the study, 400 neurologists were required in order to perform the study. Assuming that one third of neurologists who agreed to participate in the study would not actually recruit patients, the target number of neurologists was 600.

Two populations were retained for analysis. These were the intention to treat (ITT) population, corresponding to all included patients who respected the eligibility criteria, and the per protocol (PP) population, corresponding to all patients in the ITT population who completed both study visits. If a patient returned for a second visit before three months or if treatment with zonisamide was stopped between the two follow-up visits, the patient was not included for analysis.

The results of this study were principally descriptive. Demographic and clinical variables were described as mean $\pm$ standard deviation (SD) and median (range) values for quantitative variables, and as numbers and frequencies (%) for categorical variables. When statistical testing was performed, categorical variables were compared with the χ^2 test or Fisher's exact test and quantitative variables with Student's t-test or with the Mann-Whitney U-test. All statistical testing was two-tailed and a probability threshold of 0.05 was taken as statistically significant. All data were analysed using SAS 9.1 software (North Carolina, USA).

Ethical considerations

The study was performed within the framework of the Declaration of Helsinki guidelines for clinical research and according to current French regulatory requirements. Written informed consent was obtained from each patient. No patient was offered any financial incentive to participate in the study. Since patient care was not altered by inclusion in the study, and since no special procedures were envisaged for participants in the context of the study, ethics committee approval was not necessary. Procedures for data collection and management were approved by the *Conseil National d'Informatique et Liberté (CNIL)*, which ensures that all medical and personal information is kept confidential and anonymous.

Role of the funding source

This study was initiated and funded by EISAI SAS, manufacturers of zonisamide. EISAI SAS was responsible for study design, conduct, monitoring, data analysis, preparation of the study report, and initiated the preparation of this article. Operational management of the study and data analysis were delegated by EISAI to ITEC Services (Cenon, France), an independent clinical research organisation. EISAI enlisted an academic steering committee (SD, AB and GL) to advise on the design and implementation of the study and on the analysis and interpretation of the results, for which the committee members received consultancy fees from EISAI. The committee had full access to the study data and were actively involved in the preparation of the present article. The study sponsor funded editorial support from a medical writing agency (Foxymed, Paris, France) for the preparation of the present article and contributed, together with the scientific committee, to the revision of the different drafts of the manuscript. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Participating neurologists and patients

In total, 132 neurologists participated in the study and each included at least one eligible patient.

A total of 476 patients had consulted a participating neurologist and had been treated with zonisamide as adjunctive AED treatment for at least three months before Visit 1 (*figure 1*). Of these, 473 (99.4%) patients fulfilled the inclusion criteria and were eligible to participate in the study. Three patients were excluded from the study, namely 1 with generalised epilepsy, 1 aged <18 years, and 1 receiving zonisamide as monotherapy. Of the 473 eligible patients, 45 (9.4%) could not be evaluated. Of these, the CRF was incomplete for 30 patients, 13 patients had not been treated

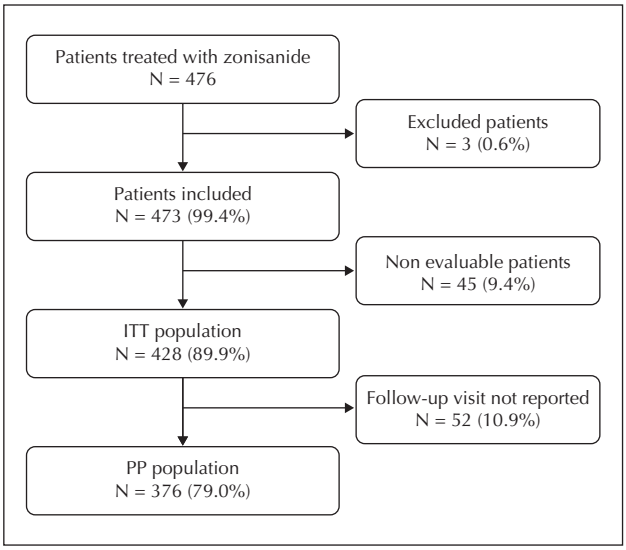

Figure 1. Patient disposition during the study.

continuously for at least three months before inclusion, the time window of three to six months between inclusion and follow-up had not been respected for eight patients, and three patients apparently had no seizures before initiation of zonisamide treatment (these reasons were not necessarily mutually exclusive). The remaining 428 patients (89.9%) constituted the ITT population. Of these, 52 patients did not attend the two follow-up visits. The remaining 376 patients thus constituted the PP population.

Patient characteristics at inclusion

The demographic and clinical features of both total and ITT populations are presented in *table 1*. The mean age of the ITT population was 42.5 years and there were more female than male patients. In accordance with the protocol, focal epilepsy had been documented for the entire ITT population (428 patients). The most common seizure type was complex partial seizure (54.0%; *n*=231). It should be noted that 12 patients presented with mixed seizure types. At inclusion, the majority of patients had been diagnosed with complex partial seizures. Around one third of patients were on long-term sickness benefit due to their epilepsy.

At Visit 1, patients eligible for analysis (ITT population) had been treated with zonisamide for at least three months (mean duration of 5.9±5.9 months). At the time zonisamide was started, the mean seizure frequency was 17.3±43.9 seizures/month (median: 6; range: 1-600). Prior to starting zonisamide, 292 (68.2%) patients had been previously treated unsuccessfully with at least two other AEDs and 158 (36.9%) with at least four other AEDs. The most frequently prescribed of these previous AED treatments were valproate (47.2% patients), levetiracetam (34.6%), carbamazepine (31.8%), topiramate (26.2%), barbiturates (25.5%), lamotrigine (22.9%), and gabapentin (22.0%).

Zonisamide treatment regimen

Zonisamide treatment was initiated at a median dose of 50 mg/kg (mean: 47.7±31.2 mg/day; range: 12.5-300 mg/day). The majority of patients (*n*=261; 61.0%) initiated zonisamide treatment at the recommended starting dose of 50 mg, whereas 136 (31.8%) patients started at the lower dose of 25 mg/day, and 21 (4.9%) at the higher dose of 100 mg/kg. The daily maintenance dose prescribed was 100-175 mg in 54 (14.3%) patients, 200-275 mg in 98 (26.1%), 300-375 mg in 110 (29.2%), and 400-500 mg in 98 (26.1%) patients. Eight patients received a daily dose <100 mg/day and a further 8 a daily dose higher than 500 mg/day. The median maintenance dose was 300 mg/day. The requested data on the titration regimen used were not analysed due to the small number of participants who completed this section of the CRF correctly. The most frequently cited reasons for choosing zonisamide were improvement of epilepsy in 338 (79.0%) patients, availability of a novel therapeutic option in 245 (57.2%) patients, and good tolerability in 200 (46.7%) patients.

At the time of initiation of zonisamide, 151 (35.3%) patients were taking one other AED and 271 (63.3%) were taking two other AEDs. Six patients did not take any AED (1.4%) at baseline. The median number of concomitant AEDs prescribed was two and maximum was five (in five patients). The AEDs most frequently associated with zonisamide were levetiracetam, valproate, lamotrigine, carbamazepine, and topiramate (*figure 2*). In patients prescribed with two AEDs, association with levetiracetam was the most frequently cited combination (9.6%).

Overall, 52 patients (12.1%) discontinued zonisamide treatment before the last study visit, after a mean treatment duration of 158±111 weeks at a mean daily dose of 234±157 mg. The principal reasons for premature treatment discontinuation were poor tolerability (21 patients), inadequate efficacy (10 patients), or both (11 patients).

Effectiveness

The effectiveness of zonisamide was assessed over two reference periods, the first covering the period between initiation of zonisamide and Visit 1 (retrospective data) and the second covering the period between Visit 1 and Visit 2 (prospective data). Prior to initiating zonisamide, the mean seizure frequency was 16.0 seizures per month (*table 2*). This frequency was reduced to 8.7 seizures/month at Visit 1 and 7.1

Table 1. Patient characteristics.

	Total population *n*=476	**ITT population *n*=428**	**PP population *n*=376**
Age at inclusion (years)			
Mean±SD	42.1±14.9	42.5±14.9	42.9±15.1
Median (range)	40.0 (17.0-88.0)	40.0 (18.0-88.0)	40.0 (18.0-88.0)
Gender			
Male	219 (46.1%)	196 (45.9%)	177 (47.2%)
Female	256 (53.9%)	231 (54.1%)	198 (52.8%)
Time since diagnosis (at inclusion; mean ± SD; years)	NA	18.2±15.0	NA
***Seizure type*[1]**			
Simple partial seizures	143 (30.0%)	135 (31.5%)	120 (31.9%)
Complex partial seizures	253 (53.2%)	231 (54.0%)	197 (52.4%)
Secondary generalised partial seizures	92 (19.3%)	84 (19.6%)	70 (18.6%)
Seizure frequency (per month) before initiating zonisamide			
Mean±SD	17.3±43.9	17.1±42.5	16.0±42.6
Median (range)	6.0 (1.0-600.0)	6.0 (1.0-600.0)	5.0 (1.0-500.0)
Long-term invalidity	150 (31.6%)	136 (31.9%)	119 (31.7%)
Associated symptoms			
Behavioural symptoms	122 (25.7%)	110 (25.8%)	100 (26.7%)
Cognitive symptoms	210 (44.2%)	192 (44.9%)	168 (44.7%)
Loss of autonomy	216 (45.6%)	197 (46.1%)	175 (46.5%)

SD: standard deviation.
[1]After review by the steering committee of the study. These categories are not mutually exclusive.

seizures/month at Visit 2. Response rates, defined as patients whose seizure frequency decreased by ≥50% compared to before initiation of zonisamide, were 61.9% at Visit 1 and 65.9% at Visit 2. The proportion of patients free of seizures at the two study visits was 31.1% (mean seizure-free period: 109.8±104.8 days) and 25.6% (mean seizure-free period: 192.1±125.9 days), respectively. An increase in seizure frequency was documented in seven patients (2.3%) between initiation of zonisamide and Visit 1, and in a further 28 patients (8.3%) during Visit 2.

Cognitive and behavioural symptoms were both considered to have improved between initiation of zonisamide and Visit 2 in 32 patients (8.5%). Deterioration was observed in 20 patients (5.3%) for cognitive symptoms and 15 (4.0%) patients for behavioural symptoms. Patient autonomy was considered to have increased in 60 patients (16.0%) and decreased in 17 (4.5%).

At Visit 1, 278/418 (66.5%) patients considered that their epilepsy had improved since starting zonisamide. This proportion was very similar at Visit 2 (245/370 patients; 66.2%). Epilepsy was considered to be worse since starting zonisamide for 23 patients (5.5%) at Visit 1 and 28 patients (7.6%) at Visit 2. Using the visual analogue scales, mean scores were 62.0±25.5 and 63.4±28.2 for impact of treatment on epilepsy scale and 59.8±25.2 and 61.6±28.3 for impact of treatment on quality of life scale at Visit 1 and Visit 2, respectively. At Visit 2, mean VAS scores of patients who considered that their

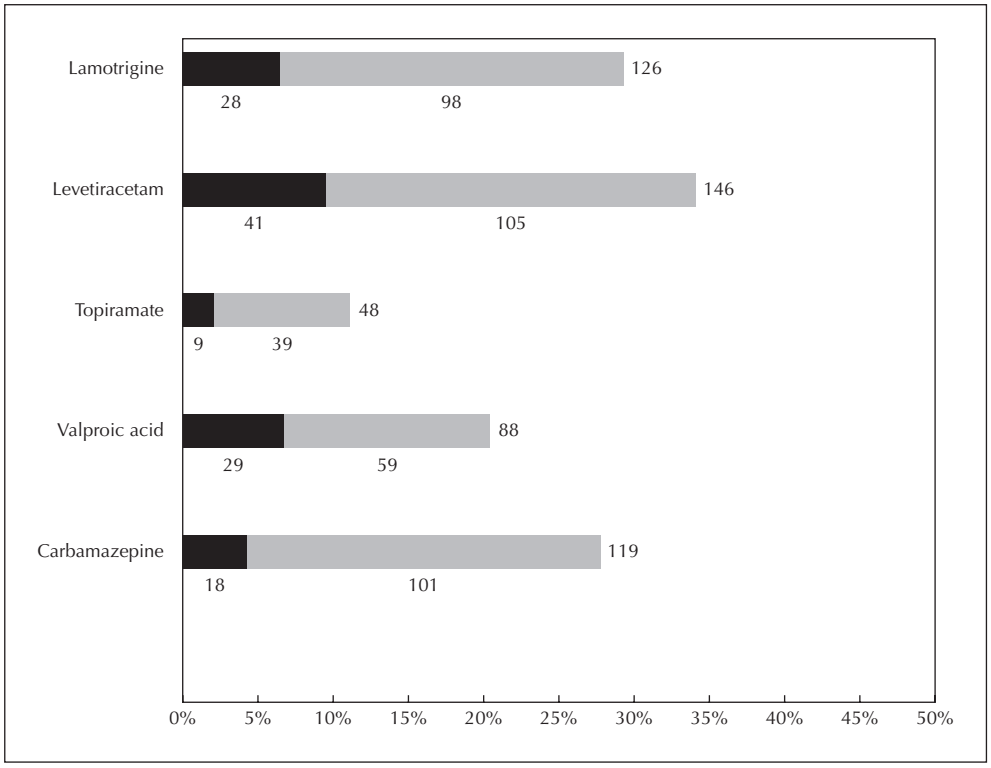

Figure 2. Other concomitant AEDs used with zonisamide.
The black bars indicate the proportion of patients using only a combination of zonisamide and the AED indicated (dual-therapy).

epilepsy had improved was 76.8±17.7 for the impact of treatment on epilepsy scale and 74.7±18.3 for the impact of treatment on quality of life scale. In contrast, for patients who considered that their epilepsy had worsened, the respective VAS scores were 18.9±23.3 and 16.1±22.7.

At the end of the study period, 36 neurologists (9.6%) considered stopping zonisamide altogether and 80 neurologists (23.7%) considered changing the zonisamide treatment regimen, generally by increasing the dose (66 neurologists).

Subgroup analyses

Subgroup analyses were performed to investigate the impact of zonisamide treatment on seizure frequency according to seizure type, seizure frequency, intensity of AED treatment regimen, and invalidity (incapacity to work because of epilepsy or other disease). Seizure frequency and responder rates before initiating zonisamide and at Visit 2 are presented in *table 3*.

With respect to seizure type, the frequency of seizures at Visit 2 decreased significantly ($p<0.05$) in all subgroups except the simple partial seizure type subgroup. Responder rates were >60% in all analysed subgroups, with no significant difference between subgroups. The proportion of patients achieving seizure freedom differed significantly between subgroups ($p<0.05$) and was greatest in the secondary generalised focal seizure group.

The proportion of patients free of seizures was significantly higher for patients receiving dual therapy compared to those who were prescribed more than two AEDs ($p=0.007$). The difference in response rates, although numerically higher in the dual therapy group, was not statistically significant.

Association of zonisamide with other AEDs

When comparing different AED combinations, response rates differed somewhat, being higher in patients prescribed zonisamide and valproate or carbamazepine compared to those prescribed zonisamide in combination with lamotrigine, levetiracetam or topiramate (*table 4*). However, these differences were not statistically significant. The proportion of patients who remained seizure-free appeared to be higher when using the combination of zonisamide with valproate or levetiracetam, compared to other combinations, although patient numbers in the subgroups were low and this observation should be interpreted with caution.

Table 2. Seizure frequency at inclusion and during follow-up.

	Before initiation of zonisamide *n*=376	**At Visit 1 *n*=376**	**At Visit 2 *n*=376**
***Responder rates*[1]**	-	*n*=291 180 (61.9%)	*n*=270 178 (65.9%)
Seizure-free patients	-	*n*=299 93 (31.1%)	*n*=308 79 (25.6%)
Number of seizures (per month)	*n*=372	*n*=365	*n*=364
≤12 seizures	267 (71.8%)	309 (84.7%)	313 (86.0%)
12-30 seizures	45 (12.1%)	26 (7.1%)	22 (6.0%)
≥30 seizures	60 (16.1%)	30 (8.2%)	29 (8.0%)
Total seizure frequency (per month)	*n*=372	*n*=365	*n*=364
Mean±SD	16.0±42.6	8.7±25.9	7.1±15.0
Median (range)	5.0 (1.0-500.0)	2.0 (0.0-304.0)	2.0 (0.0-150.0)
Changes in seizure frequency		*n*=309	*n*=336
Frequency decreased	-	302 (97.7%)	308 (91.7%)
Frequency increased	-	7 (2.3%)	28 (8.3%)

SD: standard deviation.
[1]Decrease in seizure frequency of ≥50%.

No interaction between treatment response and pre-treatment seizure frequency or invalidity was observed.

Tolerability

During the titration phase, 106 patients (24.8%) reported at least one adverse event. The most frequently reported adverse events were somnolence in 22 patients (5.1%), fatigue in 15, weight decrease in 14, and asthenia in 11 patients. Adverse events tended to appear early on after starting zonisamide, with no evidence of a dose-response relationship (data not shown). No particular combination of zonisamide with another AED appeared to be less well tolerated than another, although it should be noted that adverse events were documented in 3 of the 7 patients treated with zonisamide and topiramate. During the maintenance phase, 95 patients (22.2%) reported at least one adverse event; most frequently somnolence in 18 patients (4.21%), weight decrease in 17, and asthenia and irritability each in eight patients. Serious adverse events were reported by three patients during the initiation of zonisamide and Visit 1 (retrospective data). One patient reported an acute psychotic disorder followed by hospitalisation for delirium, another reported agranulocytosis, and another reported weight loss of 12 kg. Two patients with cancer died before Visit 2. There were no documented cases of Stevens-Johnson syndrome or blood dyscrasias. One case of kidney stones was reported in a patient treated with zonisamide in combination with gabapentin.

Weight was measured systematically for all patients at each study visit. Overall, between initiation of zonisamide and Visit 2, no change in weight was observed for the majority of treated patients (313; 86.5%). Thirty-nine patients (10.8%) lost weight and 10 (2.8%) put on weight.

During the course of the study, a total of 52 (12.1%) patients discontinued zonisamide treatment, most frequently due to the occurrence of adverse events (*n*=34; 65.4%). Information on adverse events leading to treatment discontinuation was not collected.

Table 3. Frequency of seizures according to subgroup analyses.

	Before initiation of zonisamide *n*=376	**Visit 2 *n*=376**	**Responder rates at Visit 2**	**Seizure-free at Visit 2**
Seizure type				
Simple partial seizures only	*n*=41	*n*=41	*n*=33	*n*=35
Mean±SD	34.0±96.9	9.6±26.4	26 (78.8%)	15 (42.9%)
Complex partial seizures only	*n*=144	*n*=144	*n*=99	*n*=115
Mean±SD	15.5±41.3	7.9±15.1	66 (66.6%)	20 (17.4%)
Secondary generalised seizures only	*n*=38	*n*=38	*n*=26	*n*=32
Mean±SD	3.2±5.3	1.3±2.5	17 (65.3%)	17 (53.1%
Number of seizures (per month)				
<30 seizures	*n*=312	*n*=312	*n*=228	*n*=259
Mean±SD	6.6±5.9	3.4±6.2	150 (65.8%)	71 (27.4%)
≥30 seizures	*n*=60	*n*=60	*n*=40	*n*=45
Mean±SD	64.8±91.4	26.5±27.6	27 (67.5%)	5 (11.1%)
Treatment with zonisamide as				
Bitherapy	*n*=130	*n*=130	*n*=95	*n*=106
Mean±SD	9.2±18.5	3.9±14.4	76 (80.0%)	35 (33.0%)
Polytherapy	*n*=232	*n*=232	*n*=162	*n*=188
Mean±SD	20.0±52.1	8.9±15.4	94 (58.1%)	38 (20.2%)
Invalidity				
Yes	*n*=119	*n*=119	*n*=82	*n*=93
Mean±SD	26.1±69.9	11.1±17.1	43 (52.4%)	16 (17.2%)
No	*n*=256	*n*=256	*n*=188	*n*=215
Mean±SD	11.0±17.7	5.0±13.5	135 (71.8%)	63 (29.3%)

SD: standard deviation.

Table 4. Treatment response as a function of AED combinations.

	Responder rates at Visit 2	**Seizure-free at Visit 2**
Zonisamide + carbamazepine	9/11 (81.8%)	4/12 (33.3%)
Zonisamide + lamotrigine	15/19 (79.0%)	4/21 (19.0%)
Zonisamide + levetiracetam	19/26 (73.1%)	12/29 (41.4%)
Zonisamide + topiramate	4/6 (66.7%)	2/6 (33.3%)
Zonisamide + valproate	16/17 (94.1%)	9/20 (45.0%)

Data are presented for the PP population at Visit 2.

Discussion

This study describes the use of zonisamide in "real-world" clinical practice in France, where it is licensed for the adjunctive treatment of focal epilepsy with or without secondary generalisation in adult patients. The patients included in the study had epilepsy for a mean disease duration of 18 years. In spite of the fact that the majority had previously been treated with at least three AEDs, their epilepsy was poorly-controlled and relatively severe, with a mean seizure frequency of 16 seizures/month. The majority of patients included in the study presented with complex partial seizures (54.0%), and this reflects the relative prevalence of different types of partial seizure in the adult epilepsy population in France (Picot *et al*., 2008). In addition, it has been reported in several previous studies that around one third of patients continue to have seizures, despite treatment with AEDs at the appropriate dose (Kwan and Brodie, 2002).

This study suggests that many neurologists do not follow the current recommendations when treating focal epilepsy in adult patients with zonisamide. The approved prescribing information recommends initiating zonisamide at a daily dose of 50 mg. The dose should then be increased to 100 mg/day over one week to reach a maximum dose of 500 mg/day, if necessary. In the sample studied here, around one third of patients were started on a lower dose (25 mg/day). During the maintenance phase, less than 15% (14.5%; *n*=62) of patients were being prescribed a daily dose lower than 200 mg/day, of whom less than 2% (1.9%; *n*=8) received a daily dose lower than 100 mg/day. The same proportion of patients (1.9%; *n*=8) were being prescribed a daily dose higher than the recommended dose of 500 mg/day. The median daily maintenance dose reported in our study was relatively low (300 mg/day). The results showed that 24 (19.5%) neurologists participating in the study complied with the recommended starting dose, the recommended maintenance dose, and the recommended titration procedure.

With regard to effectiveness, only 23 patients (5.4%) discontinued due to a lack of efficacy and less than 8% of treated patients considered that their epilepsy had worsened during the study. Seizure frequency was significantly decreased at both Visit 1 (p=0.0052) and Visit 2 (p=0.0002), compared to the period before initiation of zonisamide. The percentage of patients achieving $\geq$50% reduction in seizure frequency was 65.9% at Visit 2, of whom 25.6% achieved seizure freedom. This responder rate and particularly the proportion of patients who achieved seizure freedom are both higher than those reported previously. For example, based on the phase III randomised clinical trials of zonisamide, responder rates of 34.5 and 46.6% were reported using a daily dose of 300 mg and 500 mg, respectively, with less than 10% of patients achieving seizure freedom (Brodie *et al*., 2005). Nevertheless, the responder rates reported in another recent open-label observational study, the ZEUS study (Dupont *et al*., 2010), were intermediate between those reported in the pivotal clinical trials and in the present study, with a responder rate of 40.9 and 15.0% seizure-free patients. This difference may be attributable firstly to inaccurate reporting of seizures or recall bias in our naturalistic study, where information regarding the occurrence of seizures prior to treatment was provided solely from a retrospective patient report at Visit 1 and not ascertained, and secondly to the inclusion in our study of a substantial proportion of "less severe patients" (267 [71.8%] patients had $\leq$12 seizures per month before initiation of zonisamide).

Using the visual analogue scale, we observed that patients considered their quality of life to be significantly improved following initiation of zonisamide treatment. This is consistent with findings of other studies using disease-specific quality of life scales such as the QOLIE-31, which have shown that zonisamide can improve quality of life in patients with focal epilepsy (Brodie *et al*., 2005; Dupont *et al*., 2010; Helmstaedter *et al*., 2011). A high proportion of neurologists (90.4%) intended to continue prescribing zonisamide to their patients after the end of the study, indicating a positive perception of the benefit-risk profile of zonisamide.

Very few data are available to assess the cognitive and behavioural impact of new AEDs. In our study, we specifically invited patients to rate the progression of their cognitive and behavioural symptoms on a 5-item checklist before and after initiation of zonisamide. The majority of patients reported no change in their cognitive and behavioural symptoms, suggesting that zonisamide was not associated with any detrimental effect on cognitive or behavioural symptoms.

The study demonstrated that zonisamide was relatively well-tolerated, with adverse events being documented in less than 25% of treated patients, with a slightly higher rate being observed during the titration phase. This rate was lower than that reported in both ZEUS and the Phase III clinical trials (Schmidt *et al*., 1993; Faught *et al*., 2001; Sackellares *et al*., 2004; Brodie *et al*., 2005; Dupont *et al*., 2010). This difference may be due to the fact that only spontaneously-reported adverse events, considered by the investigator to be possibly or probably related to treatment, were documented in our study. Moreover, zonisamide was initiated at a dose less than or equal to the recommended dose in almost all participating patients, which may also contribute to the lower than expected adverse event

rate. The most frequently reported adverse event was somnolence, consistent with the known tolerability profile of zonisamide (Baulac, 2006; Kothare and Kaleyias, 2008). The patient who was reported to have an acute psychotic disorder, followed by hospitalisation for delirium, suffered from mental retardation and was treated with levetiracetam and valproate, in addition to zonisamide. No cases of Stevens-Johnson syndrome or blood dyscrasias, which are the principal adverse events of concern that have been associated with zonisamide treatment (Kothare and Kaleyias, 2008), were reported. In addition, no unanticipated safety issue was identified.

A number of subgroup analyses were performed. There was no interaction between seizure type and frequency, or seizure type and reduction in seizure frequency. One third of patients were prescribed zonisamide with only one other AED, most frequently levetiracetam. There was some suggestion that patients treated with a combination of zonisamide and a single other AED responded better to zonisamide than those receiving multiple AEDs, although it should be noted that the epilepsy of the latter group was more severe before starting zonisamide treatment, with a higher baseline seizure frequency.

The study has several strengths and limitations. The strengths include the relatively large number of patients (428 patients analysed) and the relatively low proportion of included patients who were not available for analysis (10%). In addition, the protocol specified that eligible patients had to take zonisamide for at least three months at the time of inclusion. The reason for this was to ensure that the neurologists' decision to prescribe zonisamide had been taken prior to participation in the study, thus limiting inclusion bias or changes in prescribing patterns due to participation in the study. Nonetheless, 29 of the 428 patients (6.8%) included in the study had been treated with zonisamide for only two and half months before the inclusion. However, it was decided that these patients should be included since this protocol violation was considered to be minor and would not be a source of inclusion bias, and also since the number of patients concerned was low. The limitations include the relatively low participation rate; patients were included in the study by less than 10% of neurologists who were contacted. Secondly, we failed to obtain exploitable data on the titration regimens used. This reduces the strength of the study regarding whether the treatment modalities used by participating neurologists were consistent or not with prescribing recommendations for zonisamide. Finally, as indicated above, the clinical data relating to the period before starting zonisamide were obtained retrospectively, thus the quality of this data cannot be ascertained.

It is important to note that zonisamide has now been approved in Europe as monotherapy for the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy, following demonstration of its efficacy in a large randomised controlled study (Baulac, 2012). Other naturalistic studies describing the use of zonisamide for this new indication should be performed in the future.

In conclusion, in everyday practice, zonisamide has been principally used in association with other AEDs for the treatment of complex focal epilepsy in adults. As most adverse events appear during the titration phase, this should be monitored carefully and physicians should be diligent in respecting the recommended titration protocol. In such patients, zonisamide appears to be effective in improving seizure control and quality of life and is generally well-tolerated.

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References

Arzimanoglou A, Ben-Menachem E, Cramer J, Glauser T, Seeruthun R, Harrison M. The evolution of antiepileptic drug development and regulation. *Epileptic Disord* 2010; 12: 3-15. doi: 10.1684/epd.2010.0303.

Baulac M. Introduction to zonisamide. *Epilepsy Res* 2006; 68(S2): S3-9.

Baulac M, Brodie MJ, Patten A, Segieth J, Giorgi L. Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurol* 2012; 11: 579-88.

Brodie MJ, Duncan R, Vespignani H, Solyom A, Bitenskyy V, Lucas C. Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; 46: 31-41.

Dupont S, Striano S, Trinka E, *et al*. Flexible dosing of adjunctive zonisamide in the treatment of adult partial-onset seizures: a non-comparative, open-label study (ZEUS). *Acta Neurol Scand* 2010; 121: 141-8.

Faught E, Ayala R, Montouris GG, Leppik IE. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures. *Neurology* 2001; 57: 1774-9.

Helmstaedter C, Stefan H, Witt JA. Quality of life in patients with partial-onset seizures under adjunctive therapy with zonisamide: results from a prospective non-interventional surveillance study. *Epileptic Disord* 2011; 13: 263-76. doi: 10.1684/epd.2011.0459.

Kothare SV, Kaleyias J. Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety. *Expert Opin Drug Metab Toxicol* 2008; 4: 493-506.

Kwan P, Brodie MJ. Refractory epilepsy: a progressive, intractable but preventable condition? *Seizure* 2002; 11: 77-84.

Picot MC, Baldy-Moulinier M, Daures JP, Dujols P, Crespel A. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. *Epilepsia* 2008; 49: 1230-8.

Sackellares JC, Ramsay RE, Wilder BJ, Browne TR 3rd, Shellenberger MK. Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures. *Epilepsia* 2004; 45: 610-7.

Schmidt D, Jacob R, Loiseau P, *et al*. Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. *Epilepsy Res* 1993; 15: 67-73.