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Complaints associated with the use of antiepileptic drugs: results from a community-based study

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Summary

Background: Few data exist with respect to the occurrence of chronic side effects due to antiepileptic drugs (AED) in routine clinical practice.
Objective: To evaluate the prevalence of subjective complaints which patients with epilepsy regard as side effects of their AED treatment in a community-based population.
Methods: Cross-sectional study. Subjects were identified through the database of AED-use in the pharmacies in a suburban area in The Netherlands. Respondents completed a brief questionnaire about their epilepsy, including a checklist with 30 complaints, which are common in AED users.
Results: We present data of 346 responding adults with treated epilepsy from a population of 107,000 adult inhabitants. Eighty percent was using monotherapy, with few patients taking new AEDs. Almost 60% of the patients reported complaints probably due to side effects in at least three domains. General CNS-related side effects were reported most often; memory problems (21.4% of the patients) and fatigue (20.3%) were dominant. Polytherapy was associated with more side effects than monotherapy. We identified differences in profiles of complaints between valproate, carbamazepine and phenytoin monotherapy. Complaints were not substantially associated with ongoing seizures or other treatment factors.
Conclusions: The majority of patients taking AEDs for epilepsy think they have side effects form their drugs, even when seizures were in remission and when monotherapy was used. Our findings suggest a need to improve monitoring of complaints of side effects of AEDs and to explore the feasibility of interventions aimed at reduction of such complaints in everyday clinical practice.

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CNS, central nervous system; PHT, phenytoin; VPA, valproate

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Introduction

Antiepileptic drug (AED) treatment aims at controlling seizures without inducing side effects. All AEDs have the potential to cause central nervous system (CNS) dysfunction and other side effects.[1–3] Patients consider avoiding side effects a very important issue in epilepsy treatment.[4] Side effects are also a crucial factor determining the willingness of patients to take drugs at long-term.[5] There is no generally accepted method of assessment for many side effects related to the use of AEDs (such as fatigue or dizziness). Gold standards for quantification of occurrence, severity and tolerability of side effects are seldom available.[2,6] Therefore, the clinician often has to rely in medical decision-making on the patient's subjective reporting.

Most information about the impact of side effects has been obtained from clinical trials. This information may have been biased. In- and exclusion criteria are often stringent. The side effects are those reported in a well-structured environment of a trial, which is distinctly different from normal clinical practice. The monitored side effects are the effects at short-term, given the relatively short duration of clinical trials. Furthermore, physicians may be more alert to detect objective, biological side effects (e.g. rash, weight gain) than subjective side effects.

We embarked on a cross-sectional study, to evaluate complaints associated with the use of AEDs with maximum effort to avoid selection bias. We identified adult AED users in one area through local pharmacy databases. We mailed all identified AED users a questionnaire asking them to confirm that they had epilepsy. We report a cross-section of the respondents' subjective complaints that are probably due to their AED treatment. We had no access to clinical records, hence information with respect to diagnosis and treatment was limited.

Methods

Seventeen of the 18 outpatient pharmacies in the Gooi-Noord region, a suburban area South-East of Amsterdam with approximately 107,000 inhabitants >15 years, co-operated. We identified all pharmacy-clients using AEDs in the pharmacy databases. The only pharmacy which did not participate (due to lack of time) has about 5000 clients. Patients with epilepsy living in institutions, such as nursing homes or homes for mentally retarded were excluded. After identification, the pharmacies mailed a questionnaire to all eligible clients (>15 years of age), with an accompanying letter explaining the purpose of the study and enclosing a prepaid return envelope. Patients who responded remained anonymous to the investigators. A number of articles in local newspapers paid attention to the study, encouraging people to respond. For medical ethical reasons, we sought no further contact with non-responders. The Medical Ethics Commission of the Gooi-Noord Hospital approved the study.

In the questionnaire, the subjects were firstly asked to confirm that they used AEDs for epilepsy, and not for another reason. Subjects without epilepsy or those who were not willing or able to complete the questionnaire were asked to return it without further comment in the prepaid envelope. The questionnaire for respondents with epilepsy focused on information about their epilepsy and included a simple checklist to report side effects of the treatment (see addendum). The responses on the checklist were categorised from 'none', via 'mild' and 'moderate/serious' to 'very serious'.

Specific questions addressed the following issues:

Did you have any (major or minor) seizures in the past 2 years, if so, how many seizures (major and minor rated separately) in the past year?
Do you find your ongoing seizures acceptable, meaning that you don't consider it necessary to do something about them when this was possible?
Have you discussed your epilepsy with a physician in the past 2 years, if so when was the last visit and how many times this last year did you discuss epilepsy with your treating physician? Who prescribes the medication, do you have personal contact with your prescribing doctor or do you receive repeat recipes without further personal contact (e.g. from the doctors secretary)?

From the pharmacy database we received data on age, gender, and AEDs the respondent was using at the time of completing the questionnaire. However, these databases did not provide information about a client's diagnosis. Hence, further information with respect to the validity of the diagnosis, the average duration of epilepsy at the time of the questionnaire and the length of time the patients were treated with the actual drugs, co-morbidity, or classification of epilepsy or seizures was not available. Because we expected that most patients taking AEDs for another reason than epilepsy, would in fact suffer from psychiatric disorders for which AEDs can be indicated, we excluded these patients from our study.

Statistical analysis

Because of the exploratory character of this study, when analysing the responses to the side effects

checklist, we dichotomised complaints as not present ('none' or 'mild') or present ('moderate/serious' or 'very serious'). Data were analysed using SPSS, with standard parametric (descriptive) statistics. For testing the differences between the several drug groups non-parametric analysis of variance was used, based on the Kruskall Wallis test. If this yielded statistical significance, post hoc comparisons between the separate groups was allowed, using Mann—Whitney *U* tests. In addition correlational analysis was performed to inspect which factors were related to side effect complaints, using linear regression analysis. For correlations Spearman's rho was used. All *p* levels were set at .05.

To evaluate whether our sample was biased by non-response, basic demographic characteristics and data on AEDS use of the non-responders (with and without epilepsy, as for these subjects there was no confirmation of the diagnosis) were inspected. This showed no differences with respect to age, gender or type of AEDs: non-responders: mean age 51.0 years (S.D. 16); responders 51.9 years; S.D. 18.9; $p = .84$; gender: men 54% (50.4% for the responders; $p = .93$); AEDs 77% monotherapy; 23% combination therapy (responders: 80.9%, 19.1%, respectively; $p = .63$).

Results

The database identified 692 patients using AEDs. These patients all received a questionnaire of which

Table 1 General characteristics of the patient group ($N = 346$).

Characteristic	
Age	51.9 years (S.D. 18.9; range 16—94)
Male	50.4%
Epilepsy (%)	In seizure remission $>$ 2 years: 170 (51%) Regular 'large seizures' 82 (24%) with an average of 3.3 seizures/year (S.D. 7.3, range 1—60) Regular 'minor seizures' 131 (38%) with an average of 75.7 seizures/year (S.D. 248.3, range 1—1820)
Are the seizures acceptable?	Acceptable: 42% of the patients
Type of treatment	Monotherapy: 80.9% Combination therapy: 19.1%
Type of AEDs (all type of treatments)	Valproate: 34.1% Carbamazepine: 30.9% Phenytoin: 21.9% Phenobarbitone: 10.4% All benzodiazepines: 2.3% Ethosuximide: 2.3% *Newer AEDs* Lamotrigine: 9.2% Oxcarbazepine: 7.5% Topiramate, gabapentin, vigababtrin and levetiracetam all: $<$1%
Type of AEDs (only monotherapy)	Valproate: 28.7% Carbamazepine: 24.7% Phenytoin: 15.7% Phenobarbitone: 3.7% *Newer AEDs* Oxcarbazepine: 5.6% Lamotrigine: 2.5% Combination therapy: 19.1%
Who prescribes the AED?	Only specialists: 83.1% Only general practitioner: 15.7%
Treatment frequency	Not in last year (only to get the prescription): 24.3% At least once in last year 75.7% (on average 2.8 times a year; S.D. 4.5)
Was epilepsy discussed with doctor during the last year?	Yes 65.8%

S.D.: standard deviation. AED: antiepileptic drug.

500 (72%) were returned. Of these patients, 101 reported not to take the AEDs because of epilepsy but for another reason (mainly psychiatric disorders and — in a few cases — migraine). The remaining 399 patients reported to take the AEDs because of epilepsy. Of these 399 patients with epilepsy, 53 refused or were unable to complete the questionnaire, leaving 346 (87%) completed questionnaires.

Table 1 shows the demographic and most important clinical characteristics of the study group. The relatively high mean age was caused by excluding patients <15 years without an upper age limit. We had no adequate data to classify their epilepsies. About half of the patients reported to be in remission for >2 years. One-fourth of the patients had 'major seizures' (seizures with longer duration and loss of consciousness such as partial complex seizures and secondary generalised tonic-clonic seizures) with an average of 3.3 seizures/year; one-fourth reported to have 'minor seizures' (such as absence seizures or myoclonic seizures) with an average of 75.7 seizures/year (about $1\frac{1}{2}$ seizure per week). Of the 166 reporting ongoing seizures, 42% considered their seizures acceptable. The large majority used one AED. Valproate and carbamazepine were the most commonly prescribed AEDs, accounting for >50% of the drugs in monotherapy. Some new AEDs (e.g. topiramate and levetiracetam) had become available only very recently in the Netherlands at the time of this study. Polytherapy was related with seizure remission (Spearman's rho .14; $p = .02$) and with frequency of minor seizures

Table 2 Subjective reported side effects ($N = 346$).

Area and type of side effect[a]	Complaints[b] (%)
General CNS	68.2 (overall CNS complaints)
Fatigue	20.3
Tiredness	18.8
General slowing	12.1
Headache	8.9
Dizziness	8.1
Motor problems	31.5 (overall motor complaints)
Tremor	13.3
Ataxia	13
Falling	5.2
Gastrointestinal complaints	33.2 (overall gastrointestinal complaints)
Weight gain	12.4
Defecation problems	8.4
Loss of appetite	5.2
Nausea	2.9
Diarrhea	2.3
Weight loss	2.0
Cognition	61.8 (overall cognitive complaints)
Memory problems	21.4
Concentration difficulties	16.1
Speech problems	8.7
Language difficulties	7.8
Visual	7.5 (overall visual complaints)
Double vision	7.5
Mood and behaviour	22.3 (overall mood/behaviour complaints)
Agitation/irritability	14.8
Depression	7.5
Cosmetic	20.4 (overall 'cosmetic' complaints)
Hair loss	7.2
Gum problems	7.8
Skin complaints	5.4
Sleep problems	8.7 (overall complaint about sleep)
Insomnia	8.7

[a] One patient may be reporting several side effects.
[b] Summary of both moderate and severe complaints.

(.28; $p = .001$). Although these both relationships were statistically significant, the correlations of .14 and .28 were moderate. Although the majority of the patients report regular appointments with a specialist in the past year, about 15% only sees a general practitioner and almost one-fourth had not seen a physician for their epilepsy in the past year. About one-third of the patients reported not to have discussed their epilepsy with the treating physician during the last year.

Table 2 summarises the results for the side effects checklist. When analysed per patient, the number of patients reporting side effects in at least three different domains was 58%. This was not restricted to respondents with ongoing seizures, i.e. both patients in remission and patients with ongoing seizures reported complaints ($p = .46$). The two domains which yielded the highest prevalence of complaints were general CNS-related complaints (such as fatigue and dizziness) with 68% complaints and cognitive complaints (62%). Within these domains, the most frequently reported complaints were memory problems (21%), fatigue (20%), tiredness (19%) and concentration difficulties (16%).

Subsequently, differences in side effect profile were tested per antiepileptic drug in four groups with >50 patients: patients on monotherapy valproate (VPA), carbamazepine (CBZ) or phenytoin (PHT) and patients on polytherapy (29, 25, 16, and 19% of the study group, respectively). Table 3 shows the areas in which these groups differed significantly. Polytherapy was associated with more side effects in most domains. PHT was associated with more concentration difficulties compared to VPA, and VPA and PHT with more weight gain compared to CBZ.

As the large effects of polytherapy may obscure possible differences between VPA, CBZ and PHT, a separate analysis has tested exclusively the difference between these three groups. Only for weight gain the Kruskall Wallis overall non-parametric test of variance yielded statistical significance (8.287; $p = .02$). This is caused by more weight gain when using VPA or PHT compared with CBZ.

Finally, we applied linear regression analysis to inspect whether possible interfering factors, such as ongoing seizures or type of care, were related to the reported complaints. We used the two dominant complaints: memory problems (21%) and fatigue (20%) as dependent variables. We entered epilepsy variables (number of 'major seizures'/year, number of 'minor seizures'/year, 2-year seizure remission, seizures acceptable or not?) and treatment variables (treatment by specialist or GP, frequency of outpatient visits and whether the epilepsy had been a discussion topic during the last year) as predictors.

For memory complaints a model was derived with only two variables. In the first step the variable '2-year seizure remission' was entered ($\beta = .16$; $p < .001$); in the second step 'are the seizures acceptable or not' ($\beta = .14$; $p = .002$). The relation-

Table 3 Differences per complaint between four groups: patients using valproate (VPA), carbamazepine (CBZ), phenytoin (PHT) monotherapy, and patients using polytherapy.

Complaint	Overall difference: Chi-square based on the Kruskall Wallis test	Differences between the four groups (VPA, CBZ, PHT, polytherapy) based on the Mann–Whitney *U* test
Fatigue	9.276; d.f. 3; $p = .03$	Polytherapy > CBZ ($U = 1834$; $p = .02$) Polytherapy > PHT ($U = 1041$; $p = .005$)
Ataxia	11.073; d.f. 3; $p = .01$	Polytherapy > VPA ($U = 2226.5$; $p = .007$) Polytherapy > CBZ ($U = 1952.5$; $p = .02$) Polytherapy > PHT ($U = 1170$; $p = .03$)
Nausea	8.389; d.f. 3; $p = .04$	Polytherapy > VPA ($U = 2334$; $p = .03$) Polytherapy > PHT ($U = 1184$; $p = .02$)
Tiredness	10.047; d.f. 3; $p = .02$	Polytherapy > VPA ($U = 2089$; $p = .02$) Polytherapy > CBZ ($U = 1724.5$; $p = .003$)
General slowing	9.830; d.f. 3; $p = .02$	Polytherapy > VPA ($U = 1995.5$; $p = .005$) Polytherapy > CBZ ($U = 1789$; $p = .009$)
Concentration difficulties	8.253; d.f. 3; $p = .04$	PHT > VPA ($U = 1799$; $p < .05$) Polytherapy > VPA ($U = 2084.5$; $p = .01$)
Weight gain	8.040; d.f. 3; $p < .05$	VPA > CBZ ($U = 3234$; $p = .05$) PHT > CBZ ($U = 1617$; $p = .004$) Polytherapy > CBZ ($U = 2117.5$; $p = .02$)

The sign > indicates a statistically significant higher percentage of patients reporting problem for that specific area.

Table 4 Summary of patient complaints (threshold > 15% of the patients complaining) for valproate (VPA), carbamazepine (CBZ) and phenytoin (PHT).

	VPA (%)	CBZ (%)	PHT (%)
Fatigue	20.5	15.1	
Tremor	**20.5**		
Tiredness	18.3	17.5	23.5
Weight gain	**21.8**		
Memory	19.4	20.1	27.4
Concentration difficulties		16.3	25.5
Ataxia			**23.3**

Bold represents areas specific per drug.

ship can be explained as follows: if the patient has ongoing seizures and does not consider the seizures acceptable there is a higher tendency to complain about memory. The percentage explained variance was extremely low (R^2 = .04), indicating that even these two variables have only a marginal relationship with reported memory complaints.

For fatigue a similar outcome was obtained. The model showed that the same two variables were related to complaints about fatigue: if the patient has ongoing seizures (β = .20; $p < .001$) and does not consider the seizures acceptable (β = .11; p = .04) there is a higher tendency to complain about fatigue. Again, the percentage explained variance was extremely low (R^2 = .05).

Finally, in an attempt to find the characteristic areas of side effect per antiepileptic drug, we summarised the complaints per AED for the three drugs with >50 patients included, i.e. monotherapy VPA, CBZ and PHT, using a threshold of 15% of the patients complaining. Results are illustrated in Table 4. Although there were some common areas (fatigue/tiredness and memory difficulties), there were also some differences: more tremor and weight gain for VPA, more concentration difficulties for CBZ and especially for PHT and more ataxia (co-ordination difficulties) for PHT.

Discussion

Physicians need to be aware if their patients taking AEDs in a routine clinical setting perceive side effects from these drugs, even when their epilepsy is well controlled. Our study of subjective side effects of AEDs used a community-based approach, taking advantage of the accurate databases of the pharmacies in the Netherlands, attempting to avoid as much as possible bias due to selecting patients at clinic visits or in trials, or in epilepsy support groups. We studied a group representative for the broad range of patients with epilepsy, living independently in the community, not actively seeking care or reporting problems. The number of 399 identified AED users with epilepsy in an area with 107,000 inhabitants of at least 15 years yields a prevalence rate of epilepsy of almost .4% within this area. This illustrates that (given the exclusion of children, patients living in institutions, and of the 5000 clients of the pharmacy which did not contribute to our study) the sample is probably representative as this comes close to prevalence rates in current epidemiological studies.[7] Although precise information on the duration of epilepsy or AED use in our respondents was not known, we have no reason to expect that the epilepsy incidence rate in this population differed from the incidence of 50 cases per 100,000 published elsewhere, making it likely that the large majority of respondents were on long-term AED treatment.

Potential flaws to our study are first of all the possible influence of non-responders and responders who did not complete the questionnaire. In our opinion, the data suggest that a reasonably unbiased sample has been enrolled. An overall 72% response to a mailed questionnaire to a heterogeneous population seems quite acceptable.[8] Basic demographic and treatment characteristics were not different for non-responders compared to responders. We have no reason to assume that response rates were very different between those with and those without epilepsy, as those with epilepsy were left free to return the questionnaire without answering the questions. Patients without complaints about their treatment may, however, have been less motivated to complete our questionnaire. As such, we may have overestimated the prevalence of complaints, but given the high response rate this is not likely to be a factor with substantial effect on the results. Clearly, we only noted complaints in patients who continued their medication and medically unacceptable side effects, such as allergic reactions usually are a reason to discontinue medication and were not the focus of this study.

Secondly, we had no detailed clinical information, independent from the information provided by the patients. Because this study was intended as a survey of AED-associated complaints in a community-based sample of AED users with a diagnosis of epilepsy, we feel the lack of detailed clinical information with respect to seizures and epilepsy does not compromise our findings. Such information typically is only reliable when studying a (specialised) clinic-based sample.

Finally, respondents may have been influenced by their knowledge of the side effects profile of their AEDs. However, there is experimental evidence suggesting such influence is limited.[9]

As can be expected in a community-based sample, treatment results in terms of seizure control were excellent for the majority of patients: almost half the patients had reached a 2-year seizure remission, 81% of the patients were using monotherapy. Only about half the patients with ongoing seizures (58%) considered their seizures unacceptable. Studies on treatment results in epilepsy have established similar results.[10] About one-third of the patients reported not to have discussed their epilepsy with his/her physician during the last year. The latter finding probably reflects the high percentage of patients in seizure remission, but might also point to a lack of expert care for some of these patients.

The aim of our study was to evaluate patient-reported subjective complaints about side effects of AEDs in a community-based sample with epilepsy. In many selected study groups of people with epilepsy, such as epilepsy support groups,[11] and in trials with refractory patients, complaints about side effects are frequent. Clearly, these groups may have been biased towards treatment resistance, and it can be expected that a community-based sample would reveal better results. Although in our sample treatment results were quite good in terms of seizure control, side effects emerged as an important issue. Almost 60% of the patients reported moderate/serious to very serious side effects on at least three areas. This finding was not restricted to a specific group, i.e. both patients in remission and patients continuing to have seizures reported complaints. We noted two domains in which complaints were especially frequent: general CNS-related side effects (such as fatigue or dizziness) and cognitive side effects. If we combine the cognitive and mood domains, behavioural complaints were the dominant complaint in our study sample. In line with this, the most frequent separate complaints were memory problems (21.4% of the patients) and fatigue (20.3%).

Comparing four major treatment groups (respectively, VPA, CBZ, PHT in monotherapy, and all using polytherapy) we found a higher percentage of complaints in patients using polytherapy. Such findings have also been reported from clinical groups,[12] studies in patients with refractory epilepsy[13] and within the context of many AED trials. In addition, we found more concentration difficulties for PHT compared to VPA and more weight gain for both VPA and PHT compared to CBZ.

It is often debated whether we may accept subjective patients complaints at face value.[4] Epilepsy may lead to secondary impairments that may cause subjective complaints. It is not always possible for patients to identify the exact source of problems, and problems may thus erroneously be interpreted by the patient as adverse effects of AEDs. Although this may be different in patients with refractory epilepsy and substantial comorbidity, our analysis showed that the most frequent complaints (memory and fatigue) had not a substantial relationship with possible interfering factors such as frequency or acceptability of seizures, or remission from seizures. Also, if we look at the type of dominant complaints per AED, we found profiles matching those established in experimental studies.[1,2] It has been stated that the use of checklists to assess side effects has the advantage of adequately addressing specific effects, and the disadvantage of causing overreporting.[14] We are aware that some complaints detected in our study may be attributable to 'background noise' or comorbidity, such as depression. It has been shown, however, that subjective complaints, measured by similar checklists as used in this study, are important determinants of quality of life in epilepsy,[11] and as such they seem clinically relevant.

The very low proportion of respondents in our sample taking new AEDs is first of all due to the time of the study, with such drugs as topiramate, gabapentin and levetiracetam having been registered only recently in the Netherlands. Secondly, most well controlled AED users in this sample would not fulfil the criteria for prescribing new AEDs according to present Dutch Guidelines for treating epilepsy. It would be interesting to study if the introduction of new AEDs with better side effects profiles would lead to a reduction in complaints in a future study using a similar instrument.

Our final conclusions are:

- The majority of patients chronically taking AEDs attribute complaints to their medication. Especially, behavioural side effects occurred frequently and may require careful monitoring and possible interventions.
- Further studies are needed to explore the mechanisms behind complaints as addressed in this study and the usefulness of interventions based on reported complaints.

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Appendix A. Side effect checklist

Questions about side effects of the medication

Antiepileptic medications can cause side effects. We would like to ask your opinion about complaints you believe to be caused by the medication.

Would you please read the list below and give your opinion by ticking the box in the row of your complaints.

	Side-effects	None	Mild	Moderate/ Serious	Very serious
1	Tiredness	O	O	O	O
2	Dizziness	O	O	O	O
3	Uncertainty when walking	O	O	O	O
4	Falling	O	O	O	O
5	Nausea	O	O	O	O
6	Defaecation problems	O	O	O	O
7	Diarrhea	O	O	O	O
8	Tremor	O	O	O	O
9	Difficulties with speech	O	O	O	O
10	Double vision, blurred view	O	O	O	O
11	Headache	O	O	O	O
12	Fatigue	O	O	O	O
13	Loss of appetite	O	O	O	O
14	Depressive feelings	O	O	O	O
15	Hyperactive behaviour	O	O	O	O
16	Loss of temper, aggressiveness	O	O	O	O
17	Slowing	O	O	O	O
18	School problems	O	O	O	O
19	Concentration diffic ulties	O	O	O	O
20	Irritability	O	O	O	O
21	Weight gain	O	O	O	O
22	Weight loss	O	O	O	O
23	Hair loss	O	O	O	O
24	Rash or other skin problems	O	O	O	O
25	Dribbling	O	O	O	O
26	Excessive hair growth	O	O	O	O
27	Gum problems	O	O	O	O
28	Sleep problems	O	O	O	O
29	Memory problems	O	O	O	O
30	Language problems	O	O	O	O

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