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Subjectively Perceived Side-Effects of Anti-Epileptic Drugs in Chronic Refractory Epilepsy

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Purpose: Antiepileptic drugs (AEDs) can cause side-effects. Patient-reported side-effects due to this type of medication are very common, but thus far only investigated in community based populations. We investigated the subjectively perceived side-effects of anti-epileptic drug treatment in patients with refractory epilepsy.

Methods: A non-selected group, of patients visiting the outpatient department between September 2011 and November 2011 was invited to complete a questionnaire only if they had experienced side-effects of their AED treatment during last year. The questionnaire, the SIDAED, assessed four different categories; cognition, mood, cosmetics and general health. Subgroup analyses were based on their medication use: mono- or polytherapy, older and newer AEDs and AEDs with a high or a low risk for cognitive and behavioral/mood side-effects.

Results: In total, 203 patients or their relatives completed the questionnaire. Mean age of the patients was 37 years (2-81). Most reported complaints (85%) were about their general health followed by cognition, mood and cosmetics. Subgroup analyses showed no differences between patients using monotherapy or polytherapy. Also, no differences were found between patients using older AEDs or newer drugs. Patients using AEDs with a high risk for side-effects did complain more about their mood but not about their cognition. Regression analysis showed that using a high risk AED for behavioral side-effects contributed significantly to the total experienced side-effects.

Conclusion: In conclusion, our study illustrates that patients are a reliable respondent to indicate side-effects despite of their refractory epilepsy. Particularly, mood complaints due to antiepileptic drugs (such as levetiracetam) are correctly noticed.

Keywords: Antiepileptic drugs; Epilepsy; Side-effects

Introduction

The best possible outcome of antiepileptic drug (AED) treatment is to achieve complete seizure freedom without adverse events. However, AEDs are frequently accompanied by a variety of side-effects. The prevalence of AED-related subjective complaints in routine clinical practice in a community-based population was almost 60% [1]. The two domains which yielded the highest prevalence of complaints are general CNS-related complaints (68%) and cognitive complaints (62%). The most frequently reported complaints within the general CNS-related domain are fatigue and tiredness. Memory problems and concentration difficulties are most frequently reported within the cognitive domain. Mood and behavioral complaints such as agitation or irritability and depression are reported less frequently (22%). Another study reported a prevalence of 67% of moderate to severe subjective complaints of patients who were considered to be well-controlled (defined as unchanged medication for the last six months) [2]. Cognitive complaints were reported most frequently. Furthermore, patients on polytherapy reported more side-effects than patients on monotherapy [1-3].

The new antiepileptic drugs such as lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), gabapentin (GBP), pregabalin (PGB) and lacosamide (LCS) seem to be similar to the older compounds in efficacy, but superior in tolerability [4]. Cognitive complaints, related to confirmed cognitive dysfunction has been reported with almost all the older drugs and especially for phenobarbital (PB), phenytoin (PHT) and vigabatrin (VGB) [4,5]. Some newer AEDs such as topiramate

(TPM) and zonisamide (ZNS) are also known to cause significant cognitive side-effects: both have diffuse cognitive effects, as well as specific effects on language and memory [5-9]. This concurs with the patient-reported cognitive side-effects that are more common with TPM, followed by ZNS and phenytoin (PHT) and are least likely to be reported with GBP, valproate (VPA), LTG and carbamazepine (CBZ) [10,11]. Furthermore, the newer anti-epileptic drug LEV is known for its high-risk to cause mood effects [12,13]. Mood side-effects are therefore most common in patients-reports with (LEV) [14,15]. The subjective reports about these drugs seem to be by and large equivalent to measured cognitive effects of these AEDs [16,17].

Negative consequences of the antiepileptic drugs necessitate interventions ranging from minor interventions such as drug switches to very expensive hospitalization. It is estimated that side-effects due to antiepileptic drugs have a major impact on health care costs which

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Received June 21, 2015; **Accepted** June 28, 2015; **Published** June 30, 2015

Citation: IJff DM, Kinderen RJ, Vader CI, Majoie MHJM, Aldenkamp AP (2015) Subjectively Perceived Side-Effects of Anti-Epileptic Drugs in Chronic Refractory Epilepsy. Adv Pharmacoeconom Drug Saf 4: 186. doi:[10.4172/2167-1052.1000186](https://doi.org/10.4172/2167-1052.1000186)

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can be as high as €20,751 (US \$26,675) per patient per year [18]. It is desirable to reduce these costs to a level as low as possible. Earlier studies already showed that side-effects are more important for patients than efficacy in long-term treatment and that long-term retention time is mainly based on subjectively perceived side-effects [19]. Previous research showed also that subjectively perceived side-effects about cognitive functions are used as a sensitive screening instrument for clinical practice which can help to identify who is at risk and needs further referral for neuropsychological assessment while keeping the burden on financial and time resources to a minimum [20]. This allows screening at an early stage and minimizes the use of expensive assessment facilities.

In addition to the community-based studies from our group [1,2,21], we attempted to investigate the impact of subjective complaints in a hospital-based study, in patients with chronic refractory epilepsy. In the community based studies most patients were in remission or they had only infrequent seizures and most were on low dose monotherapy. In the patient population of a tertiary referral center most patients have frequent seizures, are afraid of status epilepticus, and often use high dosing polytherapy. Within this study we also focused on subgroup comparisons. Firstly, a combination of AEDs can produce negative interactions which can lead to side-effects. Separate subgroup analyses were, therefore, performed to check for differences between patients on monotherapy or polytherapy. Secondly, as side-effects of AEDs are claimed to have less effects in the newer generation of AEDs, differences between the newer and older generation of AEDs were compared. Thirdly, some drugs are known to have a higher risk for side-effects than others. Therefore a high-risk group was compared with a low-risk group.

Methods

Procedure

All epilepsy patients using antiepileptic drugs, who visited our tertiary epilepsy center Kempenhaeghe, Heeze, The Netherlands, between September 2011 and November 2011, received a patient information letter by mail including an invitation to complete a questionnaire [18]. Patients were invited to complete the questionnaire only when they had experienced side-effects of the AEDs during the previous 12 months. The questionnaire could either be completed digitally via the internet or on paper. For young children and patients with severe mental retardation, proxy measures were used. All participants (patients, parents or caregivers) gave their informed consent.

Questionnaire

The questionnaire was specifically developed for this study and was subdivided into five different categories of commonly reported side-effects. The side effects of AED treatment questionnaire (SIDAED) [2], developed by our group, was used as the basis for the questionnaire. The original 10 side-effect categories of the SIDAED were compressed into four categories in order to focus on the most commonly reported side-effects. The categories used in this study were: cognition, cosmetic, mood and general health (i.e., general CNS, vision, headache, gastrointestinal, sexuality/menses complaints).

Subgroup and statistical analysis

The subgroup analyses were performed using independent t-tests with SPSS version 21.0, Chicago, IL, USA. A p-value of ≤ 0.05 was considered significant. Linear regression analysis was used to evaluate the impact of the treatment factors (mono vs. polytherapy, old vs. new AEDs and cognitive/behavioral high vs. low risk AEDs) on the total number of complaints.

Results

Demographic and clinical characteristics

In total, 1386 epilepsy patients received the request to complete a questionnaire. In total, 210 patients completed the questionnaire. Although we asked patients only to fill out the questionnaire when they had experienced any side-effect during the previous 12 months, seven patients returned the forms reporting no side-effects. These patients were excluded from the analysis, yielding a total of 203 patients reporting side-effects (14.6%).

Main characteristics of the 203 patients are shown in Table 1. Mean age was 37 years, with a range from 2 to 81 years. Most patients were treated with polytherapy (range 2-6 AEDs). Most patients used LTG as AED during the last 12 months, followed by LEV, CBZ, VPA and CLB. OXC, TPM, PHT, PGB, GBP, LCS, PB and ethosuximide (ESX) were used less frequently. AEDs that were only used by one patient were primidone, ZNS, VGB and acetazolamide. These drugs were grouped as 'other drugs' (3.0%). Most of the patients were treated with a combination of an older (such as CBZ, VPA, PB, PHT, ETX or benzodiazepines) and a newer (such as LTG, LEV, OXC, GBP, PGB, LCS, TPM) anti-epileptic drug during the last 12 months. Table 2 shows that in monotherapy LTG, VPA, CBZ and LEV are mostly used and OXC and TPM are used less frequently.

Based on the literature [16,17,22], we grouped PB, PHT, TPM, ZNS, and VGB as drugs with a high risk for side-effects. The other AEDs are grouped as AEDs with a low risk for side-effects except LEV which is known for its behavioral effect but has no cognitive side-effects [23]. Therefore, this drug is only added in the behavioral high risk group and not in the cognitive high risk group. During the last 12 months 16% of the patients used at least one of the cognitive high risk drugs and 46.8% of the patients used at least one of the behavioral high risk AEDs.

Type of side-effects

The largest group of patients (38%, $n = 78$) reported problems in three of the five categories, 24% ($n = 49$) reported to have side-effects in two of the categories, 23% ($n = 47$) reported side-effects in four of the categories, 12% ($n = 24$) reported problems in one of the five categories and five patients (3%) reported to have problems in all categories (Figure 1). Most of the patients (85%) had experienced some kind of general health side-effect due to AEDs during the last 12 months, such as sleep problems and fatigue, motor and balance problems, headache and dizziness (Table 3). Cognitive side-effects were the second most commonly reported problem among the patients (77%). Most described cognitive complaint was memory problems and to a lesser extent concentration problems, language difficulties, mental slowing and problems with information processing. Behavioral side-effects were reported in 69% of the patients. Most commonly described mood complaint was a depressive mood, irritable and angry or agitated behavior. Cosmetic side-effects such as skin rash, weight problems and gum problems occurred in 42% of the patients and 7% reported other side-effects that could not be classified. Only in the cosmetic category of the questionnaire there was a significant difference between males and females. More females reported cosmetic problems during the last 12 months ($t = -2.229$, $p = 0.027$). Only in the mood category, there was a significant negative correlation found for age ($r = -0.141$, $p = 0.044$); the younger the patients, the more mood complaints were reported.

Subgroup analyses

No differences were found between the mono- and the polytherapy group; patients on polytherapy did not report more side-effects than patients on monotherapy (Table 4). For the comparison between the

	N	%
Age mean (range)	37 (2 – 81)	
Gender		
Male	101	49.8
Female	102	50.2
Mono vs. polytherapy		
Monotherapy	67	33.0
Polytherapy	136	67.0
Number of different AEDs per patient		
Two	71	35.0
Three	40	19.7
Four or more	25	12.3
AED use during the last 12 months		
LTG	77	37.9
LEV	68	33.5
CBZ	68	33.5
VPA	65	32.0
CLB	50	24.6
Other BZP	15	7.4
OXC	27	13.3
TPM	15	7.4
PHT	10	4.9
PGB	11	5.4
GBP	8	3.9
LCS	7	3.4
PB	7	3.4
ESX	6	3.0
Other AEDs	5	2.5
Old versus new AEDs		
Old AEDs	48	23.6
New AEDs	54	26.6
Combination of old and new AEDs	101	49.8
Low risk versus high risk AEDs		
Cognitive low risk AEDs	170	83.7
Cognitive high risk AEDs	33	16.3
Behavioral low risk AEDs	108	53.2
Behavioral high risk AEDs	95	46.8

Table 1: Demographic and clinical characteristics (N=203).

	N	%
LTG	14	20.9
VPA	13	19.4
CBZ	13	19.4
LEV	12	17.9
OXC	6	9.0
TPM	4	6.0
CLB	3	4.5
PHT	1	1.5
Other BZP	1	1.5

LTG: Lamotrigine; VPA: Valproate; CBZ: Carbamazepine; LEV: Levetiracetam; OXC: Oxcarbazepine; TPM: Topiramate; CLB: Clobazam; PHT: Phenytoin; BZP: Benzodiazepines

Table 2: AED use in monotherapy patients.

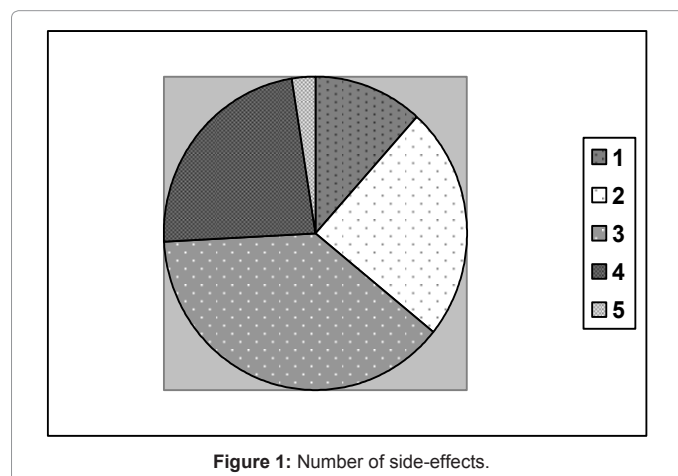


Figure 1: Number of side-effects.

older and the newer AEDs, patients who used a combination of these medication regimens were not taken into account. There were also no differences between the old and new AEDs; patients who used older AEDs did not experience more side-effects than patients who were treated with newer AEDs. Furthermore, there were also no differences between the cognitive risk groups; the cognitive high risk group did not report more side-effects than the cognitive low risk group. However, there was a significant difference between the behavioral risk groups for the mood complaints ($t = -2.776$, $p = 0.006$) and total number of complaints ($t = -2.221$, $p = 0.027$); patients from the behavioral high risk group did have significantly more problems than patients from the behavioral low risk group, especially concerning their mood.

Linear regression analysis

Thus far each comparison was made independently from the other treatment regimen. However, subgroup divisions are correlated. Therefore, regression analysis was performed with total number of complaints as dependent variable and 1) mono vs. polytherapy, 2) old vs. new AED, 3) cognitive high vs. low risk AED and 4) behavioral high vs. low risk AED as predictors. A backward procedure was used. Although both the cognitive and behavioral high vs. low risk AEDs contributed significantly (F-value: 3.044, $p = 0.05$), the procedure identified a one-factor solution as the strongest predictor of the total complaints: a behavioral high risk AED (F-value: 4.932, $p = 0.027$). The total percentage of explained variance was 2.4%.

Discussion

This study compared subjective reported side-effects among different AED treatments in a population referred to a tertiary epilepsy center. No more than 15% of the patients who visited the outpatient clinic reported to have side-effects. It is unlikely that this is due to the absence of side-effects. Rather this percentage reflects the weight the patients with chronic refractory epilepsy attribute to side-effects. Side-effects are commonly reported in community based studies in which the majority of the patients are in remission. In our population, much more importance is probably attributed to the seizures and, hence, the importance of the efficacy of the drugs.

Of the patients who did report side-effects, most had experienced some complaints in their general health, cognition or mood due to their AEDs during the last 12 months. Cosmetic side-effects occurred in a minority of the patients; more in females than males which is consistent with previous literature [24]. In our specific population, polytherapy did not induce more complaints than monotherapy. This

	N	%	Type of complaints	% *
General health complaints	172	84.7	Fatigue and sleep problems	62
			Motor and balance problems	29
			Headache	24
			Dizziness	23
			Gastrointestinal problems	14
			Nausea	13
Cognitive complaints	157	77.3	Memory problems	73
			Concentration problems	29
			Language difficulties	25
			Mental slowing	13
Mood complaints	139	68.5	Depressive mood	37
			Irritable and angry behavior	36
			Agitated behavior	20
			Mood swings	16
			Aggressive behavior	13
			Anxious behavior	5
Cosmetic complaints	86	42.4	Skin rash	45
			Weight problems	44
			Problems with gums	26
			Hair loss	15
			Itch	4
			Shaking hands	4

* Patients can have problems in more than one area.

Table 3: Type of side-effect and complaints.

Type of side-effect	mono vs. poly	Old vs. new	Cognitive low risk vs. high risk	Behavioral low risk vs. high risk
Cognition	0.772	0.699	0.492	0.235
Mood	0.549	1.000	0.305	0.006*
General health	0.466	0.955	0.614	0.843
Cosmetic	0.309	0.962	0.696	0.620
Total	0.248	0.991	0.925	0.027*

* $p \leq 0.05$

Table 4: p-Values for the different subgroup analyses.

is inconsistent with previous literature who did report more side-effects [1-3] and a lower quality of life [25] for polytherapy. This probably again illustrates a different efficacy/tolerability attribution in our patient group compared to studies in the community. Furthermore, the generation of the AEDs (older versus newer) was not relevant. The newer AEDs have been thought to have decreased the incidence of certain side-effects such as cosmetic side-effects when compared with older antiepileptic medication [24,26]. However, previous research showed that there was no difference between patients using newer versus classic AEDs in their quality of life [25]. Moreover, patients with a high-risk AED for cognitive side-effects did not complain more about their cognitive functions than patients with a cognitive low-risk AED. However, when LEV was added to this high risk AED group, patients with a high risk AED for behavioral side-effects did complain more about their mood than patients with a behavioral low-risk AED. As shown in our regression analysis, using a high risk AED for behavioral

side-effects contributed significantly to the total experienced side-effects. Note however that the percentage explained variance is low, indicating that the complaints are also related to other factors, in this group probably the epilepsy. The mood complaints of patients using LEV treatment were an essential factor in our study and are in line with a number of studies and meta-analyses [27-30]. LEV had an adverse event profile within the range of the other older drugs like PHT but with a different profile; self-reported anger and hostility were particularly frequent [13,15].

The primary limitation of our study stem from self-reporting. The side-effects were subjectively reported. Our study therefore critically relied on the validity and reliability of subjective self-report as no formal neuropsychological testing was used. Nevertheless, this is a naturalistic situation and the assessment of possible side-effects of AEDs in routine daily care of patients with epilepsy is based on these same self-reports which can be used as a sensitive screening instrument [20].

In conclusion, our study illustrates that patients are a reliable respondent to indicate side-effects despite of their refractory epilepsy. Particularly, mood complaints due to antiepileptic drugs (such as LEV) are correctly noticed.

Acknowledgements

This study is part of a PhD project which is funded by the Netherlands Organization for Health Research and Development (ZonMw), grant application number 171002204. This study has been approved by the ethics committee of the Epilepsy Center Kempenhaeghe.

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