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ORIGINAL REPORT

Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study†

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SUMMARY

Aim To assess the association between changes in medication and epilepsy-related hospitalisation.
Methods Data were obtained from the PHARMO Record Linkage System (Jan 1998 to Dec 2002). We conducted a case-crossover study among patients with a first epilepsy-related hospital admission who had continuously used at least one antiepileptic drug (AED) during a 28-week period before admission. For each patient, changes in medication in a 28-day window before hospitalisation were compared with changes in four earlier 28-day windows. Evaluated changes were: changes in AEDs (pattern and dosage), changes in interacting co-medication and changes in non-interacting co-medication (i.e. introduction of non-interacting drugs). The strength of the association between changes in medication and epilepsy-related hospitalisation was estimated using conditional logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (CI).
Results Out of 1185 patients with a first epilepsy-related hospitalisation, 217 patients met the inclusion criteria. Of the changes in antiepileptic therapy, discontinuation showed a trend towards an increased risk of hospitalisation (OR: 2.57; 95%CI: 0.81–8.17). Drug interactions influencing antiepileptic therapy rarely occurred. Introduction of three or more non-interacting drugs was significantly associated with epilepsy-related hospitalisation (OR: 4.80; 95%CI: 2.12–10.87). Of individual drugs, addition of antimicrobial agents was significantly associated with epilepsy-related hospitalisation (OR: 1.99; 95%CI: 1.06–3.75).
Conclusions Changes in AED therapy were not significantly associated with epilepsy-related hospitalisation and few drug interactions influencing antiepileptic therapy occurred. However, patients starting three or more new non-AEDs had a nearly five times increased risk of epilepsy-related hospital admission. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — epilepsy; antiepileptic drugs; hospital admission; drug interaction; case-crossover study

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INTRODUCTION

Epilepsy is one of the most common neurological disorders. The age-adjusted incidence in developed countries is around 50 per 100 000 persons per year (range 24–70 per 100 000 persons per year) and the prevalence is between 4 and 10 per 1000 persons.[1] Antiepileptic drugs (AEDs) are the mainstay of treatment. The ultimate aim of AED treatment and seizure control is the maintenance of the patients' normal lifestyle and the reduction of epilepsy-related morbidity and mortality. Optimal AED therapy can abolish seizures in 60–70% of patients with epilepsy, but in the remaining patients remission is elusive.[2,3]

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Antiepileptic drugs are selected first and foremost according to clinical efficacy, then tolerability, drug interaction profile and ease of use.[4] Although monotherapy is mostly aimed for, in up to 50% of patients, combination therapy is necessary.[5] Once the optimal treatment for the individual patient has been found, it is important to maintain the policy chosen.

However, changes in AED treatment such as dose adjustment, add-on, switch, or discontinuation may be needed or are worth trying when adverse effects are present or optimum seizure control is not yet achieved.[6] Therefore, changes in treatment may be needed to finally obtain the ideal, though delicate, balance in AED treatment. Also, changes in concomitant medication can lead to a disturbance of the balance in AED treatment. It is known that AEDs are susceptible to pharmacodynamic and pharmacokinetic drug interactions.[7,8] Most AEDs have a narrow therapeutic index, meaning that simultaneous administration of interacting drugs may result in a change in AED plasma concentration and an increased risk for adverse drug events or reduced efficacy.[9] This applies particularly to established AEDs (phenytoin, phenobarbital and carbamazepine) that are metabolised by the cytochrome P450 enzyme system. Drug interaction compendia such as 'Drug Interactions: Analysis and Management'[10] and the 'MICROMEDEX (DRUGREAX) system'[11] mention over 600 drug interactions involving AEDs. Many of these drug interactions can be potentially hazardous and are often noted as 'combination should be avoided if possible'.[10] From a pharmacodynamic point of view many drugs are known to influence the seizure thresholds.[12] Also, concomitant drugs can deregulate epileptic treatment, for instance by disturbing the metabolic balance. It is known that metabolic disorders such as hypoglycaemia can induce epileptic seizures.[13] Therefore, we were also interested in starting of new medication. Thus, changes in AEDs as well as in non-AEDs may disturb the delicate balance of AED treatment, which may lead to a reduced seizure control and a higher seizure rate possibly resulting in epilepsy-related hospitalisation.[14]

Each year approximately 7000 patients in the Netherlands are admitted to hospital because of epilepsy.[15] Until now, studies on the cause of epilepsy-related hospital admissions are scarce and often the reason for admission is unclear.[16] No studies were found on the impact of changes in medication on epilepsy-related hospital admissions. To investigate this subject we explored the association between changes in medication and epilepsy-related hospitalisation.

METHODS

Setting

The setting of the study was the PHARMO Record Linkage System (RLS). The PHARMO RLS includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950 000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards.[17] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, prescriber, amount dispensed and prescribed dosage regimen. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s in a standardised format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). Each patient is registered with an anonymous unique patient identification code that allows for the observation of patient medication in time. The database does not provide information concerning the indications for use of medicines. Our data covered the period from January 1998 to December 2002.

Study design and study population

A case-crossover study was conducted. In this design each case serves as its own control, that is each case contributes one case window and one or more control windows.[18] The case window is defined as the 'at risk period' preceding the event (hospital admission in our study).

The study population comprised all patients aged 18 years and older with a first primary hospital admission for epileptic seizures (ICD-9 codes 345.0–345.5, 345.7–345.9 and 780.3). Patients were eligible

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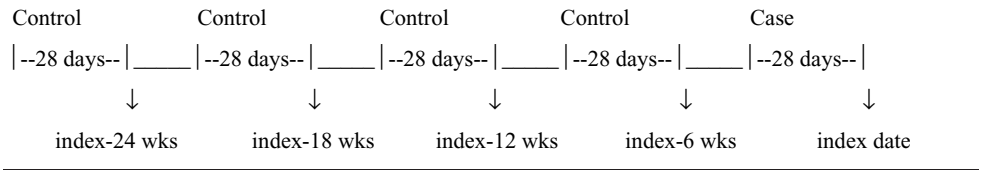

Figure 1. Case-crossover design

for inclusion when continuously exposed (80% of time) to at least one AED for a period of 28 weeks preceding the date of hospitalisation. AEDs were defined as drugs that are prescribed for epilepsy and approved for use in The Netherlands. The date of hospital admission was termed the index date. For each patient, four control moments were defined at 6, 12, 18 and 24 weeks prior to the index date. Per patient changes in medication were studied during the 28-day window prior to the index date as well as during the 28-day window prior to the control moments (Figure 1).

Determinants

Three types of changes in medication were defined. First, we studied *changes in AED therapy*; this consisted of changes in pattern (add-on, discontinuation and switch) and changes in AED dose. AED patterns were divided into four mutually exclusive groups: (1) no change in AED use, (2) add-on of another AED, (3) discontinuation of an AED and (4) switch of AEDs. Add-on was defined as a start with a new AED in combination with the AED(s) the patient was already using. Discontinuation was defined if no follow-up dispensing was recorded for at least 90 days after the theoretical end date of the last AED supply. We defined a switch of an AED if an AED was started and another AED was discontinued within the 28-day time window. Dose changes of AED were divided into three groups: (1) no change in AED dose, (2) higher dose of AED and (3) lower dose of AED.

Second, we investigated *changes in interacting drugs*. For this, we examined introduction and discontinuation of drugs that can either lead to changes in AED plasma concentration levels or affect the seizure threshold. Interacting drugs include both AEDs and non-AEDs. To identify the relevant drug interactions the following process was undertaken (Figure 2): drug interactions were selected and cross-referenced from three commonly used drug interaction compendia namely Drug Interactions: Analysis and Management,[10] MICROMEDEX (DRUG-REAX) system[11] and the Dutch Z-index.[19] AED drug interactions were selected if they were listed as 'major' or 'severe' drug interactions. From 642 drug interactions involving AEDs, 343 affected the AED efficacy or the seizure threshold and 109 of them were marked as major or severe. Drug interactions were excluded when the drug was not routinely dispensed in a community pharmacy setting (e.g. pancuronium) or when the interaction involved a product not likely to be captured by a computerised database, such as non-prescription medications (e.g. St. John's Wort). After application of these criteria 105 drug interactions remained (Table 1). Use of co-prescribed interacting drugs were categorised into four mutually exclusive groups: (1) no use of an interacting drug, (2) continued use of an interacting drug (i.e. the drug was started before the 4 weeks of observation), (3) start of an interacting drug, (4) discontinued use of an interacting drug. Start of an interacting drug was defined if a new prescription (i.e. no prior use of at least 90 days for this prescription) for this drug was started. Discontinued use of an interacting drug was defined if a patient had no new prescription for this drug 90 days after the theoretical end date. We were particularly interested

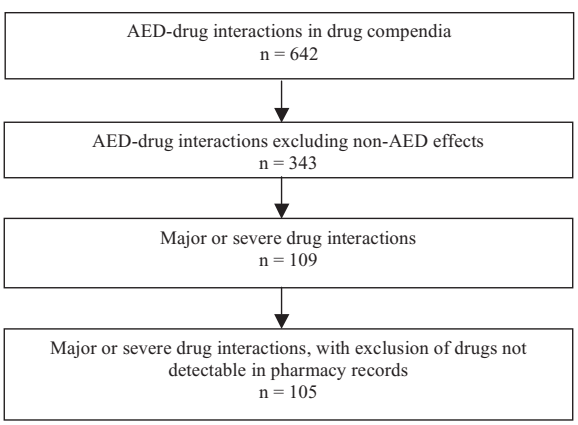

Figure 2. Selection of relevant drug interactions[10,11,19]

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Table 1. Relevant interactions with AEDs and convulsion thresholds[10,11,19]

Potential drug interaction	Interacting drugs
Lowering convulsive thresholds	antipsychotics, SSRIs, tricyclic antidepressants, maprotiline and mefloquine
Carbamazepine toxicity	acetazolamide, cimetidine, clarithromycine, danazol, diltiazem, erythromycine, fluconazole, fluoxetine, fluvoxamine, isoniazide, ketoconazole, nefazodone, propoxyphene, rifampicine, rifabutine, verapamil and vigabatrin
Primidone toxicity	valproic acid
Ethosuximide toxicity	isoniazide and phenytoin
Phenytoin toxicity	amiodarone, azapropazone, capecitabine, chloramphenicol, cimetidine, diltiazem, disulfiram, esomeprazole, ethosuximide, fluconazole, fluoxetine, fluvoxamine, isoniazide, miconazole, omeprazole, phenylbutazone, pyrimethamine, theophylline, topiramate, trimethoprim and voriconazole
Reduced phenytoin efficacy	methotrexate, rifampicine and sucralfate
Lamotrigine toxicity	valproic acid
Reduced lamotrigine efficacy	carbamazepine, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, rifampicine
Valproic acid toxicity	cimetidine and primidone

in starting and discontinuing of interacting drugs, given our objective to examine the influence of changes in therapy.

Third, we examined *changes in non-interacting concomitant medication*, that is introduction of new drugs, which were defined as no prior prescription for the same drug for at least 180 days before the dispensing date.

Potential confounding factors

As each patient served as its own control, confounding due to fixed characteristics such as genetic factors, personality, education, lifestyle and chronic diseases was eliminated by the study design. In case-crossover studies known potential confounders are usually time related. Recent hospitalisation with potential seizure related events such as stroke, head trauma etc. was considered as a potential confounding factor. Therefore, hospital admissions for cerebrovascular diseases (ICD codes 430–438), neurological diseases (ICD-9 codes 320–359) and trauma (ICD-9 codes 800–999) were compared for case and control moments.

Data analysis

Data were analysed by use of a case-crossover design. Each subject represented a matched set of data for case and control exposures. Thus, for each subject, the odds of a recent change (within 28 days) in medication before the date of hospital admission (index date) was compared with the odds of a recent change in medication before a control date. The strength of the association between changes in medication and the risk of hospitalisation was estimated using conditional logistic regression and expressed as odds ratios (ORs) with 95% confidence intervals (95%CI). Covariates were included in the regression model if they were either independently significantly associated with the outcome, or induced a 10% change or more in the crude OR for the exposure of interest on the risk of hospitalisation.

RESULTS

Of 1185 patients in our cohort with a first epilepsy-related hospital admission, 352 patients had used at least one AED prescription in the year before hospital admission. Out of this group, 217 patients met our criteria for continuous AED use. The characteristics of the study population are displayed in Table 2. Of the population 51.6% were men. The median age was 49 years. The majority of patients (57.1%) were admitted for unspecified epilepsy, followed by grand mal status epilepsy (13.4%) and generalised convulsive epilepsy (9.2%). Monotherapy was the most common AED treatment (56.2%) in our study population. The most frequently used AEDs were valproic acid, carbamazepine and phenytoin. The frequency of hospital admissions for cerebrovascular diseases, neurological diseases or trauma was low and was not different between case and control moments. This did not lead to a significant difference between case and control moments and therefore we did not adjust for this factor.

Add-on tended to be associated with a reduced risk of epilepsy-related hospitalisation, although the CI was wide (OR: 0.46; 95%CI: 0.14–1.54). We observed

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Table 2. Characteristics of the study population

Characteristics	Study population ($n = 217$)
	Number (%)
Demographics	
Male gender	112 (51.6)
Age (years)	
18–34	49 (22.6)
35–49	60 (27.6)
50–64	49 (22.6)
≥65	59 (27.2)
ICD-9 classification	
Epilepsy, unspecified	124 (57.1)
Grand mal status epilepsy	29 (13.4)
Generalised convulsive epilepsy	20 (9.2)
Partial epilepsy, no impaired consciousness	15 (6.9)
Other	29 (13.4)
Number of AEDs*	
0	3 (1.4)
1	122 (56.2)
2	73 (33.6)
3 or more	19 (8.7)
AED*	
Valproic acid	96 (44.2)
Carbamazepine	84 (38.7)
Phenytoin	61 (28.1)
Lamotrigine	22 (10.1)
Oxcarbazepine	21 (9.8)
Vigabatrine	15 (7.0)
Phenobarbital	11 (5.1)
Other AEDs	17 (7.8)

*Use 4 weeks before hospitalisation.

a non-significant increased risk of epilepsy-related hospitalisation after discontinuation of AEDs (OR: 2.57; 95%CI: 0.81–8.17). No association was found between both increased and reduced AED dosage and epilepsy-related hospital admissions (OR: 0.73; 95%CI: 0.35–1.50 and OR: 0.71; 95%CI: 0.26–1.95) (Table 3).

In 25.3% (55/217) of our study population we identified the co-prescribing of predefined interacting drugs, half of them (26/217) involving AED–AED interactions. Relevant drug interactions for our research objective by the introduction or discontinuation of interacting drugs occurred in 11% of patients (24/217). Two interactions leading to potential loss of AED efficacy occurred in case moments compared to eleven changes in control moments (OR: 0.72; 95%CI: 0.16–3.24). One interaction leading to a potential AED toxicity in the case moments versus ten in the control moments was found (OR: 0.40; 95%CI: 0.05–3.10).

Exploring the introduction of new non-interacting drugs a significant association was observed when three or more drugs were started (OR: 4.80; 95%CI: 2.12–10.87) (Table 3). Drugs that were newly started in our study population were antimicrobial agents (13%), benzodiazepines (9%), anti-inflammatory and antirheumatic drugs (7%) and antithrombotic agents (4%). For antibiotics and epilepsy-related hospitalisation the association was statistically significant (OR: 1.99; 95%CI: 1.06–3.75).

DISCUSSION

The main findings of this study are that (1) changes in AED therapy were not significantly associated with epilepsy-related hospital admissions, although discontinuation of AED therapy tended to be associated with an increased risk of epilepsy-related hospital admissions, (2) no significant association in changes of interacting drug by means of start or discontinuation of interacting drugs was found and (3) addition of three or more non-interacting drugs in patients with epilepsy was statistically significantly associated with epilepsy-related hospital admissions.

Discontinuation of AEDs has been and still is a field of discussion.[20] When epilepsy is in remission, it may be in the patients' best interest to discontinue medication to avoid side effects, drug interactions and teratogenicity. On the other hand, one should assess the risk of recurrent seizures. Based on a meta-analysis, the risk of relapse after AED withdrawal was 25% after 1 year and 29% at 2 years.[21] Specchio *et al*.[22] found that the risk of seizure relapse after discontinuing treatment was 2.9 times that of patients continuing treatment. Our study supports the evidence of the difficulties that are associated with discontinuing AEDs.

In response to increasing cost pressures, healthcare systems are encouraging the use of and the switch to generic medicines. Both physicians and patients are concerned that the generic substitute would not be clinically equivalent with the brand name formulation.[23] This kind of change was not a topic in our current study and as such these switches are not included in our definition of changes in medication. Separately, we found that within our database only three patients switched from brand to generic AED. This small number did not allow us to further investigate this topic.

We were not able to detect important interacting drugs that could lead to epilepsy-related hospital admissions. The incidence of start or discontinuation of interacting drugs was low, despite the many drug interactions mentioned in compendia involving AEDs. We found that almost 50% of the drug interactions

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Table 3. Changes in medication among case and control moments

Exposure	Case ($n = 217$)	Control ($n = 868$)	OR (5%CI)
Changes in AEDs			
Changes in AED patterns			
Continuous use/no change	209 (96.3%)	832 (95.9%)	1.0 (ref)
Switch	0 (0%)	2 (0.2%)	n/a
Add-on	3 (1.4%)	26 (3.0%)	0.46 (0.14–1.54)
Stop	5 (2.3%)	8 (0.9%)	2.57 (0.81–8.17)
Changes in AED dosage			
No dose change	202 (93.1%)	795 (91.6%)	1.0 (ref)
Higher dose	10	53	0.73 (0.35–1.50)
Lower dose	5	27	0.71 (0.26–1.95)
Interactions (IA) that can affect AED efficacy/toxicity			
No IA or no change in IA	214	847	1.0 (ref)
IA leading to AED toxicity	1	10	0.40 (0.05–3.10)
IA leading to reduced AED efficacy	2	11	0.72 (0.16–3.24)
Introduction of new non-interacting drugs			
Number of new started drugs			
None	154	682	1.0 (ref)
1	42	145	1.33 (0.90–1.97)
2	8	28	1.40 (0.60-3.27)
≥ 3	138	13	4.80 (2.12–10.87)
Group of new drugs			
Antibiotics	15	13	1.99 (1.06–3.75)
Benzodiazepines	7	25	1.12 (0.48–2.59)
Anti-inflammatory and antirheumatic drugs	7	18	1.61 (0.65–4.00)
Antihrombotics	2	11	0.72 (0.16–3.32)

affected the non-AED (due to enzyme inducing properties) and not the AED effect itself. Furthermore, another 30% of interactions were not marked as severe or major. Nonetheless, 105 drug interactions remained (Figure 2). Novak *et al*.[24] reported an incidence of 3% of co-prescribed potentially harmful interacting non-AEDs in children on chronic AEDs. In our adult population we found a higher prevalence of interactions affecting only the AED effect, 13%. This may be because of a more frequent use of antidepressants, SSRIs and antipsychotics in an adult population. Most drug interactions are based on pharmacokinetic studies or case reports. As stated by Aronson[25] there are two classes of susceptibility, interactions to which all patients are equally susceptible and interactions that affect only a subset of individuals. By selecting only major or severe drug interactions we did not account for most of the interactions in the latter category.

Addition of three or more non-AEDs was associated with a higher risk of epilepsy-related hospitalisation. Since patients with epilepsy are at higher risk of having concomitant diseases, such as disorders affecting the nervous system or ear–nose–throat disorders, co-prescription of other drugs may often occur.[26] An existing or new disease that requires intervention with multiple drugs may be the underlying problem for epilepsy-related hospitalisation. In addition, this may also lead to an increase of physical stress, which is known as a trigger for seizures. Since a substantial number (13%) of the introduced non-interacting drugs were antibiotics, the occurrence of infections and subsequent triggering of an epileptic event can also explain the observed association.[27]

The results of this study should be interpreted in the light of its limitations. Our small sample size was one of our main limitations. In a case-crossover design there is no confounding by conditions that do not vary over time. However, irregular use of alcohol, drugs, or stress may confound the relations we observed.[28,29] Moreover, underlying focal brain abnormalities such as brain tumours and systemic metabolic derangements including hypoxia or electrolyte imbalance are also important predictive factors for seizure occurrence that could not be taken into account due to the limited clinical information provided.[29,30]

Our hypothesis was that changes in drug treatment in patients with epilepsy could trigger an epileptic seizure. However, patients with seizures do not all end-up in the hospital. With our study design we were

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only able to observe the 'tip of the iceberg'. It is unknown what proportion of the total number of seizures was not detected. It would have been interesting to know the development in total seizure frequencies of the study population, not only the ones leading to hospitalisation. Also, additional information would be helpful in asserting the reason for prescribing new drugs or changes in AED treatment.

Changes in medication were studied within a 28-day time window. This period of time was chosen for several reasons. It ensures that drugs of which intake is started or discontinued during the time window had enough time to reach steady state concentrations and it allows interactions through the cytochrome P450 system to develop. However, it is possible that this period of 28 days may have been too short for these interactions to result in clinical effects, and thus, our results may have been diluted.

Although risk factors for seizures have been studied, to our knowledge this is the first study approaching the problem from the perspective of epilepsy-related hospital admissions. In our opinion, outcome studies such as ours can broaden our view of the clinical significance of different changes in drug treatment in patients with epilepsy. Further studies are needed to explain and/or confirm our findings. In addition, studies in epileptic centres where patients are stimulated to keep seizure diaries could give more information on the change of seizure frequency that may be caused by changes in medication. We are currently setting up a clinical study to explore this subject.

In conclusion, this study showed that changes in AED therapy were not significantly associated with epilepsy-related hospitalisation and that only few drug interactions occurred. In patients with epilepsy start of antibiotics or start with multiple non-AEDs (not known to interact with AEDs), is associated with an increased risk for epilepsy-related hospitalisation. In clinical practice, health care practitioners should be aware that starting antibiotics or starting three or more new non-AEDs might be a proxy for a disturbance of the delicate balance in treatment that may exist in many patients with epilepsy.

KEY POINTS

- In patients with epilepsy, starting three or more non-antiepileptic drugs is associated with an almost five times higher risk for epilepsy-related hospitalisation.
- Starting antibiotic therapy in patients with epilepsy is significantly related with epilepsy-related hospital admissions.

REFERENCES

1. Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003; **16**(2): 165–170.
2. Cockerell OC, Johnson AL, Sander JW, *et al*. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995; **346**(8968): 140–144.
3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; **342**(5): 314–319.
4. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. *Lancet* 2000; **356**(9226): 323–329.
5. Sander JW. The use of antiepileptic drugs–principles and practice. *Epilepsia* 2004; **45**(Suppl. 6): 28–34.
6. McCorry D, Chadwick D, Marson A. Current drug treatment of epilepsy in adults. *Lancet Neurol* 2004; **3**(12): 729–735.
7. Mawer GE, Pleuvry BJ. Interactions involving new antiepileptic drugs. *Pharmacol Ther* 1995; **68**(2): 209–231.
8. Patsalos PN, Froscher W, Pisani F, *et al*. The importance of drug interactions in epilepsy therapy. *Epilepsia* 2002; **43**(4): 365–385.
9. Eadie MJ. Therapeutic drug monitoring–antiepileptic drugs. *Br J Clin Pharmacol* 2001; **52**(Suppl. 1): 11S–20S.
10. Hansten PD, Horn JR. *Drug interactions: Analysis and management*. Facts and Comparisons: St. Louis, Mo; 2001.
11. *DRUG-REAX system; Greenwood Village, Colo.: MICROMEDEX*. 2001.
12. Torta R, Monaco F. Atypical antipsychotics and serotoninergic antidepressants in patients with epilepsy: pharmacodynamic considerations. *Epilepsia* 2002; **43**(Suppl. 2): 8–13.
13. van Gelder NM, Sherwin AL. Metabolic parameters of epilepsy: adjuncts to established antiepileptic drug therapy. *Neurochem Res* 2003; **28**(2): 353–365.
14. Browne TR, Holmes GL. Epilepsy. *N Engl J Med* 2001; **344**(15): 1145–1151.
15. Prismant. *Landelijke LMR data*. 2005.
16. Irving P, Al Dahma A, Srinivasan A, *et al*. An audit of admissions of patients with epilepsy to a district general hospital. *Seizure* 1999; **8**(3): 166–169.
17. Herings R. *PHARMO: A record linkage system for postmarketing surveillance of prescription drugs in The Netherlands*. [Thesis] Utrecht: Utrecht University, 1993.
18. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000; **21**: 193–221.
19. Drug interactions Z-index; The Hague, The Netherlands Colo.: Z-index. 2005.
20. Hart Y. When can antiepileptic drugs be safely withdrawn? *J Neurol Neurosurg Psychiatry* 2002; **72**(1): 5.
21. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology* 1994; **44**(4): 601–608.
22. Specchio LM, Tramacere L, La Neve A, *et al.* Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. *J Neurol Neurosurg Psychiatry* 2002; **72**(1): 22–25.
23. Haskins LS, Tomaszewski KJ, Crawford P. Patient and physician reactions to generic antiepileptic substitution in the treatment of epilepsy. *Epilepsy Behav* 2005; **7**(1): 98–105.
24. Novak PH, Elkins-Daukes S, Simpson CR, *et al.* Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care. *Br J Clin Pharmacol* 2005; **59**(6): 712–717.

DOI: 10.1002/pds

25. Aronson JK. Classifying drug interactions. *Br J Clin Pharmacol* 2004; **58**(4): 343–344.
26. van den Broek M, Beghi E. Morbidity in patients with epilepsy: type and complications: a European cohort study. *Epilepsia* 2004; **45**(1): 71–76.
27. Sander JW, Perucca E. Epilepsy and comorbidity: infections and antimicrobials usage in relation to epilepsy management. *Acta Neurol Scand Suppl* 2003; **180**: 16–22.
28. Wolf P. The role of nonpharmaceutic conservative interventions in the treatment and secondary prevention of epilepsy. *Epilepsia* 2002; **43**(Suppl. 9): 2–5.
29. Aird RB. The importance of seizure-inducing factors in the control of refractory forms of epilepsy. *Epilepsia* 1983; **24**(5): 567–583.
30. Delanty N, French JA, Labar DR, *et al.* Status epilepticus arising de novo in hospitalized patients: an analysis of 41 patients. *Seizure* 2001; **10**(2): 116–119.

DOI: 10.1002/pds