Volume and market share of anti-epileptic drugs in the Netherlands: impact of new drugs

• Pieter Knoester, Charles Deckers, Ronald van der Vaart, Bert Leufkens and Yechiel Hekster

Pharm World Sci (2005) 27: 129–134

P. Knoester (correspondence, e-mail: p.knoester@erasmusmc.nl),
C. Deckers, Y. Hekster: Department of Clinical Pharmacy, University Medical Centre Nijmegen, Nijmegen, The Netherlands
C. Deckers: Dutch Epilepsy Clinics Foundation, Location Zwolle, The Netherlands
R. van der Vaart: Dutch Drug Information Project, Health Care Insurance Board, Amstelveen, The Netherlands
B. Leufkens: Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands

Key words
Antiepileptic drugs
ATC-DDD system
Drug utilisation
Pharmacoepidemiology
Pharmacoeconomics
The Netherlands

Abstract
Objective: In the past decade, several new anti-epileptic drugs (AEDs) were introduced in the Netherlands. These new drugs, one of which is lamotrigine, are 6 to 10 times more expensive than conventional anti-convulsants. In 1997, the high cost of lamotrigine, together with a lack of clinical data supporting its superiority over conventional drugs, prompted the Dutch Health Insurance Board to release a guideline in which the use of lamotrigine was restricted to difficult-to-treat patients. Other new drugs that were marketed after 1997 also became subject to this guideline. The utilisation of new AEDs and the cost consequences are the subject of this paper.
Methods: Data from extramurally prescribed AEDs was obtained from the Dutch Drug Information Project, which is a database containing prescriptions for about 5.5 million inhabitants of the Netherlands. This data was used to study the impact of new AEDs on volume and market share of AEDs in the period from 1995 to 2001 in the Netherlands.
Results: Between 1995 and 2001, the total volume of AEDs increased by 130%, 60% of which consisted of new AEDs. Gabapentin, lamotrigine and oxcarbazepine were the most frequently prescribed new compounds. The volume share of new AEDs increased from 5% in 1995 to 18% in 2001. The market share amounted to 21.5 million euros in 1995 and rose to 47 million euros in 2001; 80% of this increase was due to the introduction of new AEDs.
Discussion: Although in 2001 the volume share of new AEDs was still modest, their introduction has led to a strong increase in the cost. New data is emerging on the effectiveness and cost–benefit sum of the new AEDs; this may change the place in therapy of these drugs. Because of their strong potential to force up cost, the positioning of new AEDs requires further attention.

Accepted May 2004

Introduction

Pharmacotherapy represents the first-line option in the management of epilepsy, a common, heterogeneous neurological disorder. For 25 years, 4 drugs have dominated the pharmacotherapeutic arsenal: carbamazepine, phenobarbital, phenytoin and valproate. However, 30% to 40% of the patients do not become seizure-free with these conventional drugs. Furthermore, their usefulness is limited by a relatively high frequency of side effects[1,2].

The introduction of several new AEDs in the last decade has therefore been a welcome expansion of the treatment options. The new AEDs are 6 to 10 times more expensive than the conventional AEDs (Table 1). This is worth noting, as the cost of pharmacotherapy represents a main cost-increasing factor in epilepsy care[3]. Even in studies initiated before the arrival of new AEDs, drug costs accounted up to 40% of the immediate medical costs[3,4].

Lamotrigine was registered in the Netherlands in 1995. The introduction of lamotrigine was followed by a period of prolonged compassionate use, as it became fully reimbursed only after the establishment of a guideline for restrictive use by the Dutch Health Care Insurance Board (CVZ) in August 1997[5]. The relatively high acquisition cost of lamotrigine, and a lack of clinical documentation in favour of lamotrigine in treating epilepsy, were the main criteria for the CVZ to issue this prescribing guideline. This guideline allows full reimbursement of lamotrigine only for patients diagnosed with epilepsy with whom at least three treatment strategies with conventional AEDs had failed.

The guideline also applies to new AEDs introduced after lamotrigine. These drugs were therefore reimbursed shortly after their introduction. The aim of the present study is to estimate the impact new AEDs have on volume and cost of anti-epileptic drugs in the Netherlands. In order to study the utilisation of antiepileptic drugs in the Netherlands, data were obtained from the Dutch Drug Information Project (GIP).

Method

Data on drug utilisation

The GIP is a unit of the CVZ, whose goal is to collect and interpret information on drug use in the Netherlands. The GIP database contains complete information on extramurally prescribed, reimbursed drugs dispensed by pharmacists and GPs with in-house pharmacies. Ten selected health insurance companies provide the data. This data refers to the 5.5 million inhabitants who are covered by the Dutch National Health Service, which amounts to about 55% of all inhabitants thus covered. The data is extrapolated to the entire insured population, i.e., those either with National Health Service or with private health insurance. For this extrapolation, coefficients have been ascribed to each collaborating health insurance company, based on patient characteristics and consumption differences between those covered under the compulsory National Health Scheme and privately insured patients. Each prescription in the GIP database contains information on the number of filled drug units, the number of dispensed defined daily doses, gender and age of the patients and the type of prescribing physician. All prescription drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification[6].

Table 1 *Anti-epileptic drugs in the Netherlands*

Year of introduction	*Name*	*ATC*	*DDD (mg)*	*Drug cost*[a]
1912	Phenobarbital (PB)	N03AA02	100	2.41
1938	Phenytoin (PHT)	N03AB02	300	2.73
1958	Ethosuximide (ESM)	N03AD01	1250	15.45
1964	Carbamazepine (CBZ)	N03AF01	1000	14.73
1971	Valproate (VPA)	N03AG01	1500	23.88
1975	Clonazepam (CLZP)	N03AE01	8	12.13
1990[b]	Vigabatrin (VGB)	NO3AG04	2000	78.55
1991	Oxcarbazepine (OXC)	N03AF02	1000	37.43
1995	Lamotrigine (LTG)	N03AX09	300	100.12
1996	Felbamate (FBM)	N03AX10	2400	198.43
1999	Topiramate (TPM)	N03AX11	300	125.72
1999	Gabapentin (GBP)	N03AX12	1800	109.13
2001	Levetiracetam (LVT)	N03AX14	2000	143

[a] Cost in euros for 30 DDD (monthly total cost for average adult dose based on most frequently used oral dosage form). Source: GIP database.
[b] In this article, anti-epileptic drugs introduced from 1990 onwards are regarded as new AEDs.

Information was obtained from the GIP database on all dispensed antiepileptic drugs (ATC-code: N03, Table 1) in the period from 1995 to 2001. The following drugs marketed in the Netherlands after 1990 were classified as new AEDs: felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate and vigabatrin. All other drugs with ATC-code NO3 were classified as conventional AEDs.

Statistics and definitions

The statistics on drug consumption and cost are presented as an average of the total insured population. Drug consumption is expressed as the number of defined daily doses (DDD) per 1000 insured persons per day. The DDD is a technical unit of measurement, usually based on the average dosage per day for the main indication in adult patients[6].

The market share is presented as a total cost. The total cost can be broken down into two major components: the prescription drug cost and the dispensing fee. The cost is expressed in euros (exchange rate on 4 November 2003: EUR 1 = USD 1.15 or GBP 0.69).

Results

Consumption

Table 2 presents the utilisation data of antiepileptic drugs in the Netherlands during the period 1995 to 2001 in DDD per 1000 insured persons per day. The consumption of anti-epileptic drugs increased from 5.4 DDD per 1000 insured persons per day in 1995 to 7.0 DDD in 2001. The conventional AEDs carbamazepine, phenytoin and valproate were the most commonly prescribed drugs throughout the study period. The use of phenytoin decreased, however, from 1.28 DDD per 1000 insured persons per day in 1995 to 0.96 in 2001.

New AEDs account for 60% of this increase, with 0.96 DDD per 1000 insured persons per day. The volume share of new AEDs increased from 0.27 DDD per 1000 insured persons per day (5%) in 1995 to 1.2 DDD (17.5%) in 2001.

For the first years after the introduction of lamotrigine, its volume of consumption remained low, at 0.04 DDD per 1000 insured persons per day in 1997. After 1998, lamotrigine started to gain market share; in 2001, the volume share was 6%. Another strong volume increase in AEDs was seen when gabapentin reached 0.25 DDD per 1000 insured persons per day in the second year after its introduction.

In 2001, gabapentin, lamotrigine and oxcarbazepine were the most frequently used new AEDs, and their consumption is still increasing. Compared with these 3 drugs, the consumption of topiramate remained relatively low at 0.08 DDD per 1000 insured persons per day in 2001. The use of vigabatrin decreased from 0.18 DDD per 1000 insured persons per day in 1995 to 0.05 in the same year. After the introduction of felbamate in 1996, its consumption volume remained below 0.01 DDD per 1000 insured persons per day.

Cost

In 1995, the total cost amounted to 21.5 million euros, of which conventional AEDs accounted for 83% (17.8 million euros). In 2001, the total cost more than doubled when 47 million euros was spent on AEDs. A major share (80%) of this 25.5 million euros cost increase is accounted for by the introduction of new antiepileptic drugs. The market share of the new AEDs increased from 3.8 million euros in 1995 (17%) to 24.2 million euros (52%) in 2001. During the study period, the cost per DDD went up from 0.7 euros per DDD in the period 1995–1997 to 1.2 euros per DDD in 2000, a 63% increase. As Figure 1 shows, until 1997 the development in costs trailed behind the volume development; after 1997, the cost of AEDs increased strongly in relation to consumption. Both 1998 and 2001 showed peak increases in the cost, with relative increases of 123% in both years. The first peak increase coincided with the changed reimbursement policy regarding lamotrigine. In 1998, when 4.1 million euros were spent on lamotrigine, that drug accounted for 74% of the increase costs. The strong rise in gabapentin use is the major factor for the peak increase seen in

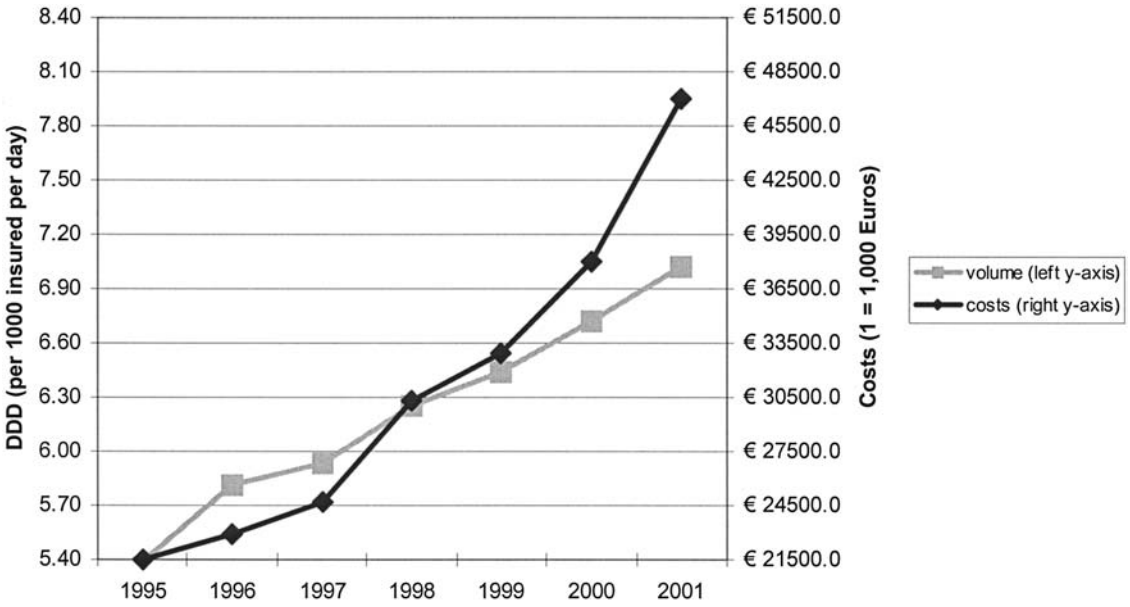

Figure 1 *Patterns in cost and volume of AEDs in the Netherlands.*

2001. The cost for gabapentin rose by 5 million euros in 2001, which accounted for 56% of the total increase in pharmaceutical costs in that year. The volume and cost shares of individual AEDs in 2001 are presented in Figure 2. The overall picture is that new AEDs have a relatively small volume share, but a comparatively high share of pharmaceutical costs. Lamotrigine, for instance, had a volume share of 6% in 2001 whereas its contribution to total pharmaceutical costs, 24%, was the highest of all AEDs.

Discussion

Drug utilisation data provides useful information to health care professionals and policy makers on different areas of interest[7]. Several other researchers have also studied antiepileptic drug utilisation[8–13]. Our study has the same two limitations as some of the others. First, we used DDD data to determine utilisation. This does not provide insight into the percentage of people who are exposed to AEDs, nor does it give insight into the number of new cases. Some other studies counted patients to estimate the epidemiology of epilepsy. For instance, Shackleton et al. and Lammers et al. collected drug-dispensing information on an individual patient level, i.e., they knew how many patients used AEDs, in which dosages these AEDs were used and whether patients used more than one antiepileptic drug[10,11]. The counting method undoubtedly supplies more specifically epidemiological information than an aggregated measure of analysis like the DDD used in this study[7].

The other limitation of this study is that the indication for which the AEDs are prescribed is unknown. Carbamazepine and clonazepam especially are often prescribed for other indications than epilepsy. Carbamazepine and valproate are increasingly being used in the field of psychiatry. Shackleton et al. demonstrated that for almost 50% of the patients on carbamazepine monotherapy, the indication was not epilepsy[11]. In several of the epidemiological studies, corrections were made for off-label use by applying a correction factor of 0.68[8,14]. For new AEDs, the correction factor is not yet known, but it is likely that there is off-label use of these compounds as well. The effectiveness of gabapentin and lamotrigine is being assessed for several other diseases, mainly bipolar disorder and neuralgic pain[15–19]. Despite these limitations, the present study still allows a comparison to be made between the prescribing of different drugs within one class and the related cost consequences. The GIP database is based on the computerised registration of prescription drugs by several health maintenance organisations. This has the advantage of being a relatively easy, inexpensive and rapid way to collect information on drug use for a large number of patients[20]. Our study uses a much larger database than other studies did.

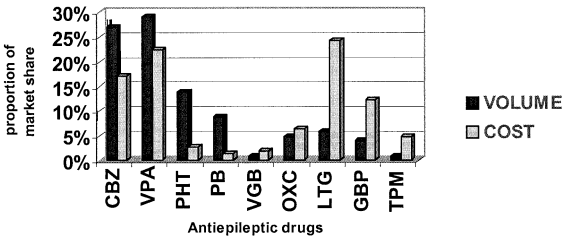

Figure 2 *Comparison of volume and cost of AEDs in 2001.*

The CVZ guideline for prescription restriction of lamotrigine confined the use of the drug to the treatment of patients with refractory epilepsy only. The guideline was issued almost two years after the registration of lamotrigine in the Netherlands, which explains the low volume share of lamotrigine in the first years after registration. Only after the reimbursement settlement in August 1997 did the volume share start to increase. Nowadays, lamotrigine is the most frequently prescribed new AED in the Netherlands.

The conventional AEDs, in particular carbamazepine and valproate, are still the most frequently prescribed

Table 2 *Utilisation data of anti-epileptic drugs in the Netherlands*

Name	*ATC-code*	*Volume share (DDD per 1000 insured persons per day)*							*Market share (per 1000 euros)*						
		1995	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*
Old antiepileptic drugs															
Phenobarbital[a]	N03AA02	0.72	0.77	0.76	0.70	0.67	0.64	0.64	603	674	654	630	686	685	674
Phenytoin	N03AB02	1.28	1.25	1.20	1.19	1.16	1.13	0.96	1,287	1,250	1,244	1,254	1,340	1,316	1,312
Ethosuximide	N03AD01	0.05	0.05	0.05	0.05	0.05	0.04	0.05	189	194	197	196	188	175	189
Clonazepam	N03AE01	0.13	0.15	0.17	0.18	0.19	0.21	0.21	859	989	1,196	1,405	1,546	1,713	1,911
Carbamazepine	N03AF01	1.69	1.79	1.75	1.80	1.84	1.86	1.87	7,671	7,471	7,229	7,584	7,849	7,794	8,061
Valproic acid	N03AG01	1.25	1.44	1.54	1.68	1.80	1.96	2.06	7,163	8,133	8,73	9,373	9,507	9,929	10,566
Subtotal old AEDs		**5.12**	**5.45**	**5.47**	**5.59**	**5.71**	**5.84**	**5.79**	**17,773**	**18,712**	**19,251**	**20,443**	**21,114**	**21,612**	**22,713**
New antiepileptic drugs															
Oxcarbazepine	N03AF02	0.09	0.17	0.22	0.28	0.32	0.34	0.38	542	970	1,269	1,618	2,216	2,748	3,073
Vigabatrine	N03AG04	0.18	0.19	0.20	0.18	0.12	0.07	0.05	3,187	3,256	3,079	2,976	2,014	1,211	909
Lamotrigine	N03AX09	–	0.0	0.04	0.19	0.28	0.36	0.43	–	14	1,081	5,207	7,506	9,89	11,381
Felbamate[b]	N03AX10	–	0.0	0.0	0.0	0.0	0.0	0.0	–	0	37	90	95	84	98
Topiramate	N03AX11	–	–	–	–	0.01	0.06	0.08	–	–	–	–	5	1,672	2,245
Gabapentin	N03AX12	–	–	–	–	–-	0.03	0.25	–	–	–	–	3	816	5,766
Levetiracetam	N03AX14	–	–	–	–	–	–	0.02	–	–	–	–	–	–	771
Subtotal new AEDs		**0.27**	**0.36**	**0.46**	**0.65**	**0.73**	**0.88**	**1.23**	**3,729**	**5,241**	**5,466**	**9,892**	**11,838**	**16,422**	**24,242**
Total AEDs		***5.39***	***5.81***	***5.93***	***6.25***	***6.44***	***6.72***	***7.02***	***21,502***	***22,953***	***24,717***	***30,334***	***32,953***	***38,033***	***46,955***
Insured persons in the Netherlands[c]		15.22	15.31	15.36	15.44	15.50	15.60	15.68							

[a] Data of primidon, methylphenobarbital and phenobarbital presented as a combined total.
[b] DDD per 1000 insured persons per day less than 0.002.
[c] 1 = 1,000,000 persons.

drugs. Their volume share continues to increase, which may also be due to off-label use. In 2001, the new AEDs accounted for 18% of the use in AEDs. Despite this still modest volume share, the impact of the new AEDs on the development of costs seems large. Over the test period, the cost more than doubled, to 47 million euros in 2001. The market share of new AEDs soared from 17% in 1995 to 52% in 2001. Lamotrigine has the highest market share at 11 million euros in 2001 (24%). A similar pattern in drug sales was seen in the United Kingdom, where the introduction of new AEDs led to a twofold increase in costs of AED prescriptions in the period 1992 to 1997[3].

At present, the utilisation of new AEDs can still be described as modest, considering that around a third of the patients have refractory epilepsy[11]. This may be due to an effective implementation of the CVZ guideline for prescription restriction among prescribing physicians, but this has not been assessed. There are also other factors that probably contribute to the modest utilisation volume of new AEDs. Petri and Urquhart described a so-called channelling phenomenon, which means prescribing new drugs to a selected group of patients[21]. In epilepsy treatment, channelling would consist of using new AEDs for intractable patients only, irrespective of a guideline. Furthermore, physicians may hesitate to prescribe new AEDs soon after registration because not all relevant data on safety is available at the moment. Felbamate and vigabatrin are cases in point. Both drugs were introduced as promising new AEDs, but as Table 2 shows, these drugs are now seldom prescribed. These two drugs are associated with severe, idiosyncratic adverse effects that became apparent only several years after the drugs had been registered[22,23].

When considering the cost consequences presented in this paper, it is important to ask whether the present positioning of the new AEDs will be subject to change in the near future. Data is emerging on the efficacy and tolerability of new AEDs in patients with newly diagnosed epilepsy[24–29]. The main advantage of the new AEDs over conventional drugs like carbamazepine and phenytoin seems to be a favourable tolerability profile, which leads to fewer treatment failures. In the case of lamotrigine, its better tolerability profile resulted in a higher quality of life for patients treated with the drug, compared with those treated with carbamazepine or phenytoin[27,30]. The results of these monotherapy trials may contribute to a more widespread use of new AEDs earlier in the treatment and thus to their being employed as first-line treatment for newly diagnosed epilepsy. Physicians may decide to switch from conventional AEDs as first-line treatment options to the new alternatives based on the lower number of treatment failures. The utilisation of phenytoin is decreasing (Table 2), possibly because physicians are changing their treatment preference towards new AEDs with fewer side-effects.

Conclusion

Unbridled use of new AEDs will inevitably impose a tremendous burden on the healthcare budget. A well-regulated healthcare environment will increasingly mandate a demonstration of value for money, defined in terms of measurable health and/or financial outcome for a given pharmacotherapeutic option. Selection criteria for the rational use and positioning of new AEDs are needed, criteria which should be based on effectiveness and cost-benefit data derived from real-life use. Without data on population-based effectiveness of new AEDs, plan payers, like the CVZ, will remain wary about paying for new drugs or reconsidering the positioning of these drugs. Drug utilisation studies should be included in the ways of finding criteria that attribute to a rational positioning of the new antiepileptics and in demonstrating that new AEDs, when effective, will *almost always* justify their cost.

Disclosure

This study is part of the research project on rational use of lamotrigine. This project received a grant from the Netherlands Health Care Insurance Board. Neither the Board nor any other organisation exerted undo influence on the results of this work.

Conflicts of interest

None of the authors have financial ties to any pharmaceutical company.

References

1 Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. N Engl J Med 1992; 327: 765–71.

2 Mattson RH, Cramer JA, Collins JF et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985; 313: 145–51.

3 Heaney D. The pharmacoeconomics of the new antiepileptic drugs. Epilepsia 1999; 40 (Suppl) 8: 25–31.

4 Kotsopoulos IA, Evers SM, Ament AJ et al. Estimating the costs of epilepsy: an international comparison of epilepsy cost studies. Epilepsia 2001; 42: 634–40.

5 Trenite DG, Rentmeester TW, Scholtes FB et al. Peri-marketing surveillance of lamotrigine in the Netherlands: doctors' and patients' viewpoints. Pharm World Sci 2001; 23: 1–5.

6 World Health Organization, Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. Oslo: WHO, 1998. Ref Type: Report

7 Mantel-Teeuwisse AK, Klungel OH, Verschuren WM et al. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. J Clin Epidemiol 2001; 54: 1181–6.

8 Beghi E, Monticelli ML, Monza G et al. Antiepileptic drugs as 'tracers' of disease. A calculation of the prevalence of epilepsy through an analysis of drug consumption. The Group for the Study of Epilepsy in General Practice. Neuroepidemiology 1991; 10: 33–41.

9 Banfi R, Borselli G, Marinai C et al. Epidemiological study of epilepsy by monitoring prescriptions of antiepileptic drugs. Pharm World Sci 1995; 17: 138–40.

10 Lammers MW, Hekster YA, Keyser A et al. Use of anti-epileptic drugs in a community-dwelling Dutch population. Neurology 1996; 46: 62–7.

11 Shackleton DP, Westendorp RG, Kasteleijn-Nolst Trenite DG et al. Dispensing epilepsy medication: a method of determining the frequency of symptomatic individuals with seizures. J Clin Epidemiol 1997; 50: 1061–8.

12 Roberts SJ, Feely M, Bateman DN. Prescribing of anti-epileptic drugs in the northern and Yorkshire region: 1992–1995. Seizure 1998; 7: 127–32.

13 Rochat P, Hallas J, Gaist D et al. Antiepileptic drug utilization: a Danish prescription database analysis. Acta Neurol Scand 2001; 104: 6–11.

14 Banfi R, Borselli G, Marinai C et al. Epidemiological study of epilepsy by monitoring prescriptions of antiepileptic drugs. Pharm World Sci 1995; 17: 138–40.

15 Botts SR, Raskind J. Gabapentin and lamotrigine in bipolar disorder. Am J Health Syst Pharm 1999; 56: 1939–44.

16 Gorson KC, Schott C, Herman R et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999; 66: 251–2.

17 Pande AC, Crockatt JG, Janney CA et al. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord 2000; 2: 249–55.
18 Simpson DM, Olney R, McArthur JC et al. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology 2000; 54: 2115–9.
19 Ichim L, Berk M, Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. Ann Clin Psychiatry 2000; 12: 5–10.
20 Meijer WE, Heerdink ER, Pepplinkhuizen LP et al. Prescribing patterns in patients using new antidepressants. Br J Clin Pharmacol 2001; 51: 181–3.
21 Petri H, Urquhart J. Channelling bias in the interpretation of drug effects. Stat Med 1991; 10: 577–81.
22 Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ 1997; 314: 180–1.
23 Pellock JM. Felbamate in epilepsy therapy: evaluating the risks. Drug Saf 1999; 21: 225–39.
24 Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999; 37: 81–7.
25 Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. 012 Study group. Epilepsy Res 1999; 34: 199–205.
26 Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996; 23: 149–55.
27 Steiner TJ, Dellaportas CI, Findley LJ et al. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. Epilepsia 1999; 40: 601–7.
28 Christe W, Kramer G, Vigonius U et al. A double-blind controlled clinical trial: oxcarbazepine *versus* sodium valproate in adults with newly diagnosed epilepsy. Epilepsy Res 1997; 26: 451–60.
29 Dam M, Ekberg R, Loyning Y et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989; 3: 70–6.
30 Gillham R, Kane K, Bryant-Comstock L et al. A double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure. Seizure 2000; 9: 375–9.