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# Prescribing of anti-epileptic drugs in the northern and Yorkshire region: 1992–1995

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Epilepsy is a condition for which regular drug treatment is normally prescribed. We have examined the primary care prescribing rates for anti-epileptic drugs (AEDs) in a region of northern England with a population of 6.8 million. Over the 4-year period 1992–1995 the number of AED prescription items issued rose by 15%. A third of this rise is accounted for by increased prescribing of the new anticonvulsants, vigabatrin, lamotrigine and gabapentin, which are primarily indicated for adjunct use. Prescribing of phenytoin and barbiturates fell over the same period, but this reduction was more than compensated for by increased prescribing of carbamazepine and sodium valproate. There were notable differences in both the overall volume and the choice of AEDs used in different health authority areas and these are probably attributable to the influence of the local secondary-care sector on the therapeutic regimens adopted by general practitioners in the area.

*Key words:* anti-epileptic drugs; primary care; prescribing rates; pharmacoepidemiology.

## INTRODUCTION

For drugs used in the treatment of a chronic condition, the rates of prescribing will depend on three main factors: the true prevalence of the condition in the population, the diagnostic (ascertainment) rate and the choice of treatment. If the relevant drugs are prescribed only, or principally, for this condition, and prevalence and ascertainment rates are reasonably uniform, then prescribing may give insight into the variability in choice of treatment.

Drug treatment is a standard approach in the control of epilepsy, and the relevant drugs are only rarely used for treating a few other limited conditions, such as post-herpetic neuralgia. This study, in the northern and Yorkshire region of England (population: 6.8 million), examines general practitioner prescribing rates for anti-epileptic drugs (AEDs), with a view to determining the temporal trends in choice of drug treatment and the extent of variability between health authority areas. Absolute rates of epilepsy prevalence are not accurately known, however for examining variability in choice of treatment the key requirement is that rates should be relatively uniform both geographically and across the duration of the study.

The prevalence of epilepsy depends on its definition. Against an agreed definition of active epilepsy (seizures of any type in the previous 2 years, or seizure-free but taking AEDs) the estimated prevalence is 0.5–1%[1–3]. The incidence of epilepsy is highest in early childhood[2], but since those who become seizure-free without drug control roughly balance incident cases in later years, the prevalence remains similar across much of the age range. However, the prevalence rises for those aged 65 or over. In the health authority areas studied this age group accounts for between 14.5 and 18% of the resident populations. Although there are gender differences in epilepsy prevalence, the areas are sufficiently large to have the same male to female population ratios. Ethnicity may affect true epilepsy prevalence or, because of cultural factors, ascertainment rates. In the United Kingdom the impact of ethnicity on epilepsy ascertainment and prevalence has not been quantified. For active epilepsy under-ascertainment by general practitioners is unlikely because of the prescribing of drugs or the occurrence of seizures. Temporal trends in prevalence are also unlikely to be a major factor over the relatively short—4 year—duration of this

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study. Assuming prevalence uniformity, the variability in per capita use of AEDs should be attributable to differences in treatment choice.

## METHODS

### Data

General practitioner prescribing of anticonvulsants (Section 4.8.1, British National Formulary[4]) and registered patient populations for the period January 1992 to December 1995 were extracted from Prescription Analysis and Cost (PACT) data aggregated at the Family Health Service Authority (FHSA) level. The quarterly number and cost of prescription items, and the quantity prescribed were obtained for each drug in each of the 16 authorities. Data for the quarter ending June 1995 was unavailable, and for the quarter ending December 1993 incomplete for Wakefield FHSA. These two quarters were excluded.

Over the study period there were more than 10,000 prescribed items for each of ten AEDs. Five of these drugs—phenytoin, carbamazepine, ethosuximide, sodium valproate and clonazepam—were examined individually. Phenobarbitone and primidone prescribing were aggregated as total barbiturate prescribing, and the three newer drugs—vigabatrin, lamotrigine and gabapentin—were also aggregated. Prescriptions for methyl-phenobarbitone (2200 items in total) were excluded from the analysis of individual drugs.

Using the number of items as a measure of prescribing volume has drawbacks, as it takes no account of possible systematic variation between areas or time periods in the average quantity prescribed per item. For analysis of individual drugs this is easily overcome by using the total quantity prescribed in grams, but for aggregation purposes some meaningful equivalence between drugs is needed. Although expressing quantities in terms of the defined daily dose[5] (DDD) is the natural choice, DDDs were not available for all the drugs in this study. Our approach was to define for each drug an 'adjusted item', being the average quantity per item (in grams) over all health districts and all quarters. The quantities prescribed in a health district each quarter were then expressed as the numbers of 'adjusted items' for individual drugs, and these units could sensibly be aggregated across drugs. Assuming that there was no systematic difference in prescription duration for primidone and phenobarbitone, the sizes of 'adjusted' items closely reflected the ratio of 250 mg primidone to 60 mg phenobarbitone expected on the basis of bioequivalence. For the newer drugs, the size of 'adjusted' items confirmed an equivalence, based on recommended daily doses, of 2000 mg vigabatrin to 1200 mg gabapentin, and indicated 175 mg as an equivalent average daily quantity for lamotrigine. This latter quantity reflects the average dose of lamotrigine across different therapeutic regimens. The advised dose[4] is 100–200 mg per day for monotherapy or prescribed with the enzyme inhibitor sodium valproate, whereas in adjunct with an enzyme inducer such as carbamazepine or phenytoin the recommended dose is 200–400 mg per day.

### Analysis

For prescribing volume FHSA rates were expressed as 'adjusted' items per 1000 registered population. In order to compare variability between different areas without confounding by temporal changes, relative rates were also calculated as the ratio of the FHSA rate to that for the region as a whole, for the same drug and time period. A similar procedure applied to analysis of cost per item.

Variability between areas was defined in non-parametric terms, to avoid undue influence from extreme rates in some instances

$$\text{quartile variation, } qv = \frac{\text{interquartile range}}{1.35 \times \text{median}} \times 100.$$

For a normal distribution, the quartile variation is equivalent to the coefficient of variation as usually defined[6].

## RESULTS

### Prescribing for the region as a whole

The overall volume of prescribing rose steadily over the 4-year period, from 26 to 30 AED items per 1000 patients per quarter. For carbamazepine items (8.6–10.7), valproate (5.0–6.6) and vigabatrin/lamotrigine/gabapentin (0.41–1.82) the quarterly rates per 1000 patients all rose; prescribing for both clonazepam (0.82) and ethosuximide (0.16) was static; and for phenytoin (7.6–7.2) and phenobarbitone/primidone (3.4–2.7) the rates fell (Fig. 1). For individual drugs, there were no significant changes over the 4-year period in the average quantity per prescription item: phenytoin 8.85 g, carbamazepine 18 g, valproate 34.3 g, clonazepam 59 mg, ethosuximide 25 g, phenobarbitone 3.00 g, primidone 24.7 g, lamotrigine 5.5 g, vigabatrin 63 g, gabapentin 38.5 g. Consequently volume trends are the same whether expressed in items or grams. The above quantities per item were used to define the size of an 'adjusted' item.

### Differences between FHSAs

In the following inter-FHSA comparisons all rates are on the basis of 'adjusted' items per 1000 population.

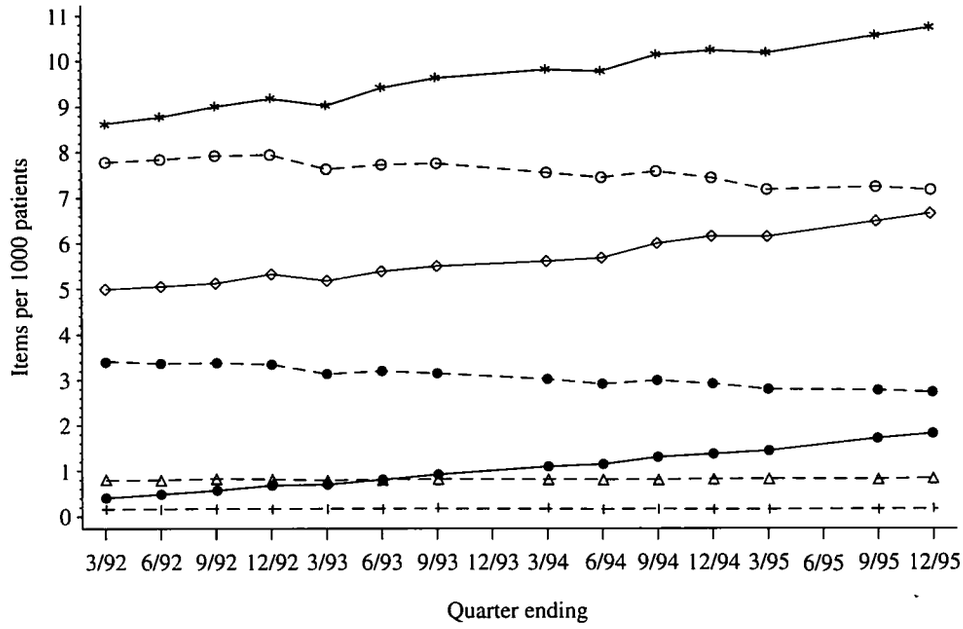


Fig. 1: NYRHA prescribing of anti-epileptic drugs (BNF 4.8.1). ○, phenytoin; ◇, valproate; • – – •, phenobarbitone/primidone; •—•, vigabatrin/lamotrigine/gabapentin; △, clonazepam; ∗, carbamazepine; +, ethosuximide.

Table 1: Anticonvulsant prescribing for quarter ending March 1992. Regional per capita rate and relative rates for FHSAs, with the four highest and the four lowest rankings indicated (except ethosuximide for which rates and ranks were highly variable between quarters)

| | Total anti-convulsants | Phenytoin | Phenobarbitone and primidone | Carbamazepine | Valproate | Clonazepam | Vigabatrin, lamotrigine and gabapentin | Ethosuximide |
|---|---|---|---|---|---|---|---|---|
| Regional rate: 'adusted' items/1000 patients/quarter | 25.95 | 7.61 | 3.38 | 8.63 | 4.95 | 0.82 | 0.41 | 0.16 |
| Inter-FHSA quartile variation (%) | 7.6 | 16.5 | 15.5 | 8.7 | 8.3 | 35.8 | 26.6 | 21.9 |
| FHSA relative rates (rank) | | | | | | | | |
| Newcastle | 1.15 (1) | 1.34 (2) | 1.13 (2) | 1.14 (2) | 0.89 (15) | 0.95 | 1.93 (1) | 0.79 (13) |
| Gateshead | 1.14 (2) | 1.35 (1) | 1.10 (4) | 1.09 (3) | 0.96 | 1.05 | 1.09 | 0.93 |
| Durham | 1.09 (3) | 1.13 | 1.01 | 1.04 | 1.04 | 1.85 (1) | 1.12 | 0.67 (14) |
| N Tyneside | 1.09 (4) | 1.25 (3) | 1.11 (3) | 1.06 | 0.96 | 0.75 | 0.80 | 0.41 (16) |
| Northumberland | 1.07 | 1.18 (4) | 1.05 | 1.04 | 0.98 | 0.72 (14) | 1.16 (4) | 1.52 (1) |
| Cleveland | 1.06 | 0.93 (13) | 0.91 | 1.27 (1) | 0.95 | 1.31 (4) | 1.38 (2) | 1.08 |
| Sunderland | 1.06 | 0.98 | 1.08 | 0.96 | 1.31 (2) | 1.56 (2) | 0.65 (16) | 0.99 |
| S Tyneside | 1.03 | 1.18 | 0.90 | 1.02 | 0.99 | 0.73 (13) | 1.09 | 0.58 (15) |
| Calderdale | 1.01 | 1.01 | 0.90 | 0.85 (15) | 1.37 (1) | 1.04 | 0.98 | 1.19 (2) |
| Wakefield | 1.00 | 1.02 | 0.84 (15) | 1.07 | 0.92 (13) | 1.32 (3) | 0.84 | 1.11 |
| Cumbria | 0.99 | 1.03 | 0.95 | 0.95 (13) | 1.05 (4) | 0.87 | 0.71 (15) | 1.08 |
| Leeds | 0.98 | 0.97 | 0.87 (13) | 1.08 (4) | 0.87 (16) | 0.97 | 1.21 (3) | 1.16 (3) |
| Humberside | 0.96 (13) | 1.10 | 1.43 (1) | 0.71 (16) | 0.91 (14) | 0.75 | 0.76 (13) | 0.98 |
| N Yorkshire | 0.94 (14) | 0.83 (14) | 0.84 (14) | 1.06 | 1.02 | 0.70 (15) | 0.76 (14) | 1.10 |
| Kirklees | 0.89 (15) | 0.74 (15) | 1.06 | 0.87 (14) | 1.08 (3) | 0.78 | 0.80 | 1.13 (4) |
| Bradford | 0.82 (16) | 0.57 (16) | 0.67 (16) | 0.97 | 1.04 | 0.63 (16) | 1.01 | 0.85 |

Relative to the region as a whole, FHSA rates for total AED prescribing changed little over the study period. The rates for the first and last quarters of the study period are shown in Tables 1 and 2 respectively. The extremes were Newcastle prescribing 115–118% of the regional per capita rate, and Bradford where relative prescribing rose from around 80% in the period up to September 1993 to around 85% over the remaining period. Inter-FHSA variability, as measured by quartile variation, increased slightly from 8 to 14%.

Tables 1 and 2 also show the FHSA relative rates for prescribing of individual drugs, and the regional per capita rates. The quartile variation gives a summary measure of the variability between FHSAs, and the ranks of the highest four and lowest four FHSAs highlight the more extreme relative rates. In general, both the relative rates and the quartile variation showed surprising consistency over the 4-year period.

Bradford (~ 60%), Kirklees (~ 70%) and North Yorkshire (83% falling to 75%) were distinctly low users of phenytoin, with the other FHSAs more

closely grouped. For the barbiturates, phenobarbitone and primidone, Bradford again had the lowest usage (65–70%), and Humberside rates were much higher than elsewhere (143% falling to 132%). Of the three FHSAs with low (~ 80%) carbamazepine prescribing in December 1995, Humberside had risen from 71% over the study period, whilst Kirklees and Calderdale had declined slightly from 85%. Throughout the 4 years, relative usage of carbamazepine was highest in Cleveland, though the gap between it and the majority of FHSAs closed considerably in the latter half of 1995, as usage elsewhere increased more rapidly. Valproate prescribing was high in both Sunderland and Calderdale throughout the 4 years, whereas in Durham usage rose faster than for the region as a whole during the last 18 months. There was wide variation between FHSAs in clonazepam usage particularly during the earlier years of the study, and Durham and Sunderland continued to have very high relative rates (160% in December 1995).

In early 1992 Newcastle usage of the three newer drugs (vigabatrin, lamotrigine, gabapentin) was distinctly higher than elsewhere but still small in absolute terms—250 items per quarter, principally vigabatrin. Because of the small volume of prescribing, relative rates were very unstable in the early period of the study. The most notable change was in Humberside where the relative rate rose from 85% in June 1993 to 120% (highest FHSA) in December 1995. Newcastle and North Tyneside were high users of vigabatrin, whereas in Leeds and Humberside the high rates derived from lamotrigine use.

Prescribing of ethosuximide was low and consequently relative rates varied greatly from quarter to quarter for individual FHSAs.

### Newer drugs

Gabapentin only came into use in the quarter ending June 1993, whereas lamotrigine was prescribed by general practitioners in the region from late 1991, and vigabatrin from 1989. The regional usage of these drugs, for a near-static population, is illustrated in Fig. 2. On the logarithmic scale used, parallel gradients indicate equal percentage growth. After steep rises for lamotrigine and gabapentin following their initial introduction, growth rates had steadied at 10 and 8% per quarter respectively by December 1995. However, the volume of lamotrigine (7408 items per quarter) was far higher than for gabapentin (2091 items). Prescribing for vigabatrin grew at the lower rate of around 2% per quarter throughout the study period, with the quarterly number of items overtaken by lamotrigine in June 1993.

### Prescribing costs

The various AEDs have wide-ranging unit costs (per daily dose) so differences between FHSAs in overall costs per prescription item are largely determined by the differences in drug mix. For individual drugs inter-FHSA variability in cost per item is influenced by the differences between FHSAs in the average quantities prescribed per item. For example, an average prescription for carbamazepine was 20.2 g in Cleveland but only 15.5 g in Newcastle. Examination of cost per gram within individual drugs revealed little inter-FHSA variation except for clonazepam. This high variability for clonazepam was due to the use of very expensive special preparations (typically £35 per item instead of £3.70, at 1995 prices) by a few practices particularly in Sunderland but also, to a lesser extent, in Northumberland and Gateshead. In December 1995 the average cost of clonazepam items in Sunderland was nearly three times the average cost regionally.

## DISCUSSION

In the present study we have not attempted to define the prevalence of epilepsy, but have examined prescribing of AEDs across 16 health authority areas over a 4-year period. Although the choice of AED will depend on the type of epilepsy, we have no reason to believe that the proportions of each type differ across the 16 areas. During this time prescribing volume increased by 15% (3.8% per annum). Possible reasons for this change include: greater use of more than one drug concurrently; a reduction in the number of patients with active epilepsy who are not using any AEDs; or increasing concerns about stopping medication in patients who have been seizure free. In the Mersey Health Region during the early 1990s an audit[7] of 31 practices identified 1341 patients (0.8%) with active epilepsy of whom 110 were not receiving AEDs, and 69% of the rest were on monotherapy. Another audit[8] of 25 general practices in Glasgow reported that 1052 (0.72%) of 145,609 patients were prescribed AEDs and of these 76% were prescribed one drug only. In our study, one-third of the observed 15% increase in AED prescribing is accounted for by increased usage of the three newer drugs, and in general these are used in adjunct with other drugs; only lamotrigine is currently licensed as monotherapy for epilepsy. Thus some of the increased usage may be attributable to polytherapy involving these drugs rather than additional patients being treated, especially as it is recognized that a significant proportion of epileptics have disease which is difficult to control.

Table 2: Anticonvulsant prescribing for quarter ending December 1995. Regional per capita rate and FHSA relative rates with the four highest and the four lowest rankings indicated (except ethosuximide for which rates and ranks were highly variable between quarters)

| | Total anti-convulsants | Phenytoin | Phenobarbitone and primidone | Carbamazepine | Valproate | Clonazepam | Vigabatrin, lamotrigine and gabapentin | Ethosuximide |
|---|---|---|---|---|---|---|---|---|
| Regional rate: 'adusted' items/1000 patients/quarter | 30.04 | 7.19 | 2.72 | 10.69 | 6.63 | 0.82 | 1.82 | 0.16 |
| Inter-FHSA quartile variation (%) | 14.2 | 21.2 | 20.3 | 13.8 | 8.3 | 26.7 | 16.4 | 28.2 |
| FHSA relative rates (rank) | | | | | | | | |
| Newcastle | 1.18 (1) | 1.36 (2) | 1.18 (3) | 1.15 (3) | 1.06 (4) | 1.09 | 1.14 (3) | 1.39 (3) |
| Gateshead | 1.15 (3) | 1.37 (1) | 1.14 | 1.14 (4) | 0.99 | 1.04 | 0.98 | 0.79 (15) |
| Durham | 1.14 (4) | 1.17 | 1.06 | 1.11 | 1.17 (3) | 1.60 (1) | 0.96 | 0.80 (14) |
| N Tyneside | 1.15 (2) | 1.33 (3) | 1.20 (2) | 1.19 (2) | 0.92 (14) | 0.83 | 1.14 (4) | 1.03 |
| Northumberland | 1.09 | 1.22 | 1.13 | 1.12 | 0.95 | 0.80 | 1.00 | 1.41 (2) |
| Cleveland | 1.10 | 1.00 | 0.96 | 1.23 (1) | 1.00 | 1.17 (4) | 1.18 (2) | 1.10 |
| Sunderland | 1.12 | 1.08 | 1.15 (4) | 1.05 | 1.26 (2) | 1.59 (2) | 1.01 | 0.83 |
| S Tyneside | 1.03 | 1.25 (4) | 0.89 | 1.02 | 0.94 (13) | 0.69 (14) | 0.91 | 0.82 (13) |
| Calderdale | 0.95 | 0.92 (13) | 0.88 | 0.81 (14) | 1.27 (1) | 0.93 | 0.83 (15) | 1.30 (4) |
| Wakefield | 1.00 | 1.13 | 0.82 (14) | 1.05 | 0.87 (15) | 1.25 (3) | 0.89 (13) | 0.98 |
| Cumbria | 1.01 | 1.10 | 1.07 | 0.96 | 0.96 | 1.08 | 0.98 | 1.43 (1) |
| Leeds | 0.92 (13) | 0.92 | 0.85 (13) | 0.97 | 0.81 (16) | 1.03 | 1.10 | 0.96 |
| Humberside | 0.97 | 1.01 | 1.32 (1) | 0.78 (16) | 1.05 | 0.72 (13) | 1.20 (1) | 0.85 |
| N Yorkshire | 0.88 (14) | 0.75 (14) | 0.80 (15) | 0.96 (13) | 0.97 | 0.69 (15) | 0.84 (14) | 0.98 |
| Kirklees | 0.83 (16) | 0.69 (15) | 0.98 | 0.78 (15) | 0.95 | 1.05 | 0.91 | 0.98 |
| Bradford | 0.84 (15) | 0.58 (16) | 0.66 (16) | 1.02 | 0.98 | 0.62 (16) | 0.69 (16) | 0.73 (16) |

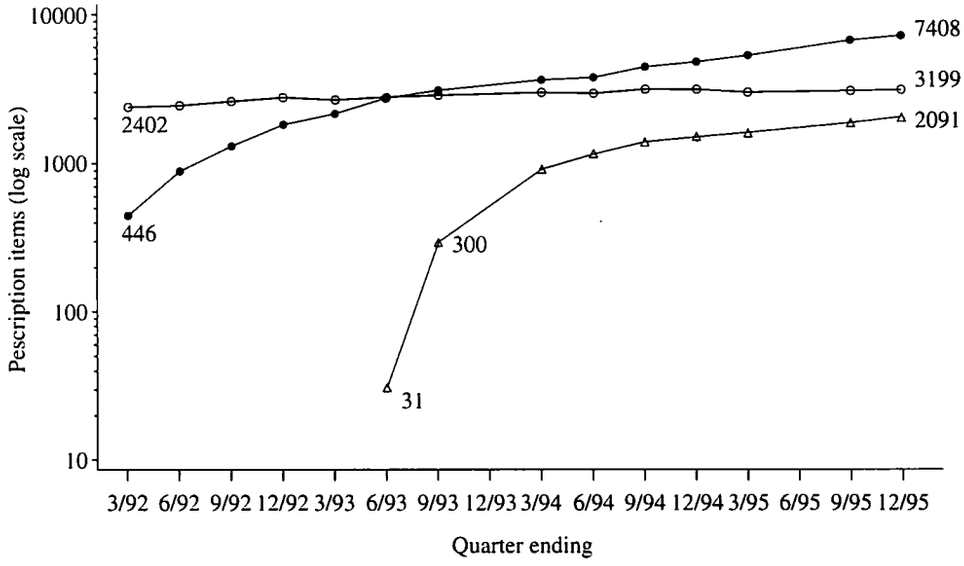


Fig. 2: Primary care prescribing of new anti-epileptic drugs in the region. ○, vigabatrin (introduced 12/89); •, lamotrigine (introduced 12/91); △, gabapentin (introduced 6/93).

Although barbiturate and phenytoin usage declined over the period (down 20 and 5% respectively), this is more than outweighed by increased prescribing for carbamazepine (up 24%) and sodium valproate (up 33%). There may have been an increase in the number of patients being prescribed AEDs, either through increased ascertainment or because they remain on therapy longer despite having become seizure free. However, the rise in AED usage may arise because, despite reports of previous trends towards a reduction in polytherapy[9], the adjunct use of the newer drugs is viewed by prescribers as legitimizing polytherapy more broadly.

Individual health authorities showed considerable differences both in the overall volume of prescribing and in their usage of individual drugs. This suggests that preferences in the secondary care sector, or possibly local treatment guidelines, may generate common influence on the choice of therapy provided in local practices. In some geographical areas prescribing is low only for specific drugs whereas in others low prescribing applies more generally. For example, carbamazepine prescribing is low in Kirklees, Calderdale and Humberside, but in Calderdale this is compensated for by high valproate usage and in Humberside by barbiturate prescribing. Usage of phenytoin is par-

ticularly low in Bradford, and since the population age breakdown is similar in Cleveland and Sunderland cannot be explained on these grounds. Kirklees and Bradford also have low AED prescribing generally. Cultural differences between ethnic groups may underlie some of this variation in AED prescribing. At the 1991 census the Asian population was 13.6% in Bradford and 8.2% in Kirklees, 3.9% in Calderdale, 3.3% in Leeds, 2.9% in Newcastle, 1.4% in Cleveland, 1% in Wakefield and less than 0.75% in the other health areas.

New drugs were taken up earlier in the teaching hospital health districts of Newcastle and Leeds. In Newcastle vigabatrin was used earlier than elsewhere, and in Leeds lamotrigine. A likely reason is the influence of neurologists in teaching hospitals in these health districts, and may be a consequence of local clinical trials. The relatively late uptake of these newer drugs in Humberside, and the particularly high phenobarbitone usage, may also be attributable to local opinion at the time of the study. Both Durham and Sunderland had higher than average prescribing for both valproate and clonazepam, with usage of other drugs running near, or slightly above, the rates for the region as a whole. This could well reflect the influence of local specialists.

The benzodiazepine anticonvulsant clonazepam shows the largest variability between health districts, with usage in Durham well over twice that in Bradford. However, the absolute quantities prescribed are still lower than for all AEDs except ethosuximide. Again this is likely to be due to local secondary care influences.

There is less apparent variability in the prescribing of AEDs by comparison with some other drugs we have investigated. For example, inter-FHSA quartile variation for $H_2$ blockers, beta-blockers, ACE inhibitors and inhaled bronchodilators is between 18 and 32%, and for oral antidiabetics, HRT, and inhaled steroids, which have more clearly defined indications for use, quartile variation is in the range 10–16% (unpublished work). None the less it is evident that epilepsy management is by no means uniform. This lends support to comments made elsewhere about quality of epilepsy care in the United Kingdom[10]. We believe that examining prescribing data of this type can be of value in assessing the role of drugs in the treatment of epilepsy within the primary care sector. It also raises important questions about the variability of management approach to this common disabling condition by hospital consultants in different areas, and suggests that agreed clinical guidelines for epilepsy would have a useful role.

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