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Short communication

Trends in the first antiepileptic drug prescribed for epilepsy between 2000 and 2010

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ABSTRACT

Purpose: To investigate changes in the choice of first anti-epileptic drug (AED) and co-prescription of folic acid after a new diagnosis of epilepsy.
Methods: We searched anonymised electronic primary care records dating between 2000 and 2010 for patients with a new diagnosis of epilepsy and recorded the first AED prescribed and whether folic acid was co-prescribed.
Results: From 13.3 million patient years of primary care records, we identified 3714 patients with a new diagnosis of epilepsy (925 children and 649 women aged 14–45 years). Comparing first time AED prescriptions in 2000 and 2001 to those in 2009 and 2010 showed a significant decrease in the proportion of carbamazepine and phenytoin prescribed and a significant increase in the proportion of lamotrigine and levetiracetam prescribed. In women aged 14–45 years, and girls aged <18 there was a significant decrease in the proportion of sodium valproate prescribed. Women aged 14–45 years were significantly more likely to be co-prescribed folic acid with their first AED compared to all other patients (20% vs 3%, p-value < 0.001). The proportion of folic acid co-prescribed with the first AED did not change significantly between 2000 and 2010.
Conclusion: The changing trends in the first AED prescribed over the last decade, particularly in women of childbearing age, reflect published evidence in terms of AED efficacy, tolerability and safety.

1. Introduction

Several factors have influenced the selection of appropriate anti-epileptic drugs (AEDs) to treat epilepsy during the last decade. The side effect profiles of older AEDs are less acceptable when compared with newer AEDs.[1] Randomised controlled trials have directly compared the efficiency and tolerability of AEDs. For example, the SANAD trial recommended lamotrigine as first line treatment for focal epilepsies and sodium valproate as the first line treatment for generalised or unclassified epilepsy.[2] Several new effective AEDs have become available e.g. eslicarbazepine acetate, lacosamide, levetiracetam, oxcarbazepine, pregabalin, rufinamide, and zonisamide. Potentially harmful effects of certain AEDs on the cognitive and physical health of the unborn and developing child are increasingly recognised – in particular sodium valproate.[3,4] National guidelines have recommended the co-prescription of folic acid with AEDs for women who may become pregnant.[5]

In the UK, every individual is assigned a National Health Service (NHS) general practitioner (GP). GPs prescribe the vast majority of AEDs in the UK. To ensure that patients with epilepsy receive the best treatment, it is important to know whether actual prescribing practice reflects current best recommended practice. A patient with epilepsy and good seizure control on an established AED is not often changed to a potentially more suitable AED, given the risk of seizure recurrence. We therefore specifically looked at the trends of first time prescriptions of AEDs using GP records in Wales, UK.

2. Methods

GP primary care electronic health records are stored within the Medical Research Council Centre for Informatics and Public Health

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Research (CiPHER) at Swansea University, UK, as part of the Secure Anonymised Information Linkage (SAIL) system.[6,7] At the time of analysis, the SAIL system had approximately 40% of the Welsh population's GP records available (around 1.1 million people).

We electronically searched all SAIL records for patients with a diagnosis of epilepsy recorded for the first time between 1st January 2000 and 31st December 2010, and who were prescribed an AED for the first time on at least two consecutive occasions within 12 months of the diagnosis date. For each patient matching these criteria, we recorded the first AED prescribed, together with their age, sex, year of diagnosis and whether folic acid was co-prescribed. (It is not possible to obtain accurately the type of epilepsy from the GP records). We grouped the data into the following age categories: children (aged 0–17 years); adults (aged ≥ 18 years) and women of child-bearing age (defined as aged between 14 and 45 years). We plotted trends in AED prescriptions and calculated correlation coefficients. We also compared the proportions of AEDs prescribed in 2000 and 2001 compared to those prescribed in 2009 and 2010. Pearson's product-moment correlation and proportion tests were calculated using the statistical software package R version 2.15.2.

Due to anonymisation issues, we excluded AEDs which constituted <2% of total prescriptions – these included ethosuximide, gabapentin, oxcarbazepine, phenobarbital, topiramate and zonisamide.

This study was approved by the HIRU information governance panel (Project 0202). The National Research Ethics Service has confirmed that HIRU projects using anonymised data do not require specific NHS research ethics committee approval.

3. Results

We analysed 13.3 million patient years of GP records (a mean of 1.2 million patients every year between 2000 and 2010) and identified 3714 patients with a new diagnosis of epilepsy who met the inclusion criteria. Of these, there were 2722 adults (aged ≥ 18 years); 992 children (aged 0–17 years); and 649 women of childbearing age (14–45 years of age). Fig. 1 shows trends in AED

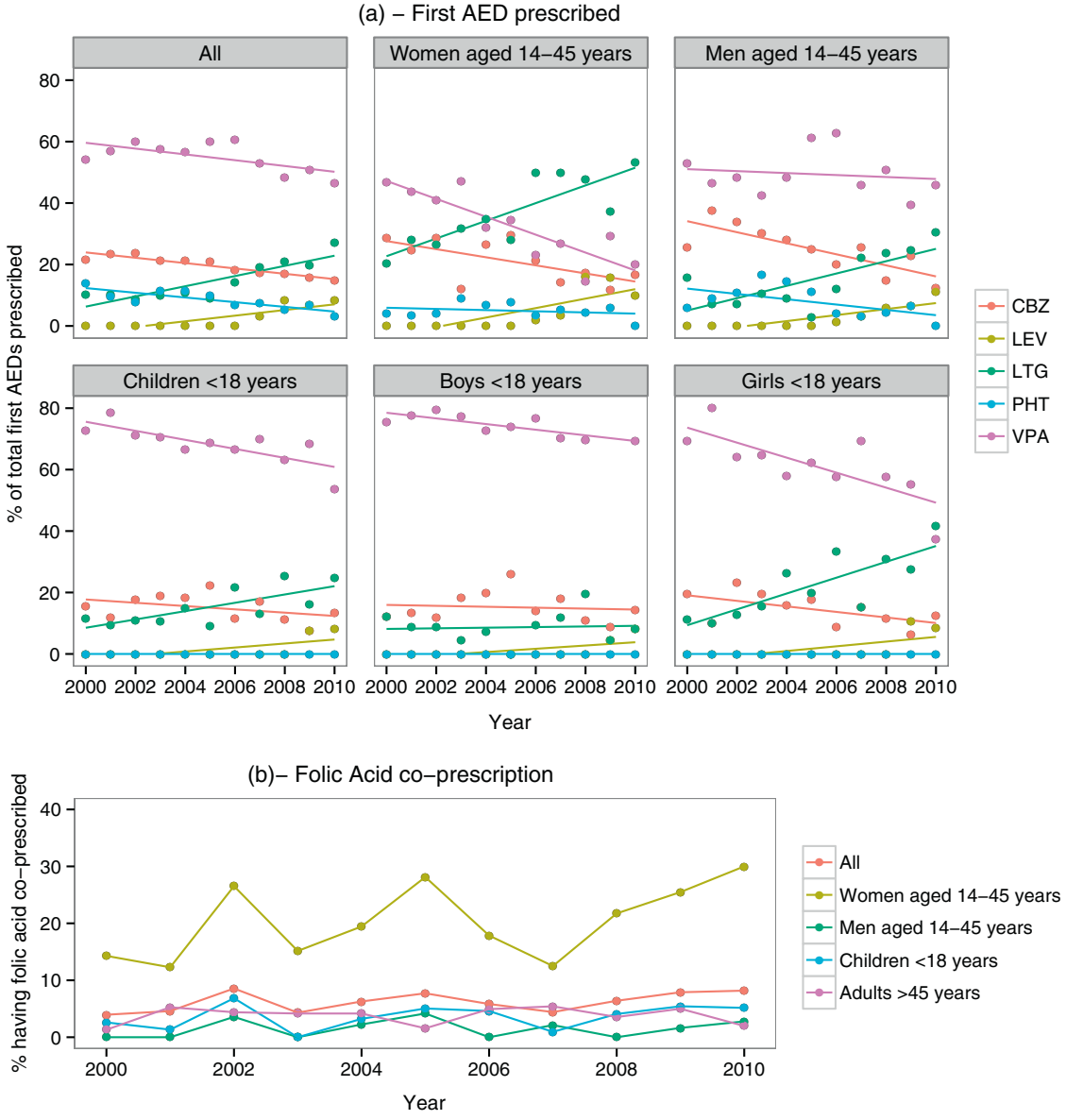

Fig. 1. (a) First AED prescribed as a proportion of all first AED prescriptions by year between 2000 and 2010. Lines represent linear regression models of the data points. (b) Proportion of first AED prescriptions having a co-prescription of folic acid between 2000 and 2010. (CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, sodium valproate).

Table 1
Number of prescriptions of each drug and folic acid in years 2000 and 2001 combined and in 2009 and 2010 combined.

Category		2000 + 2001 combined	2009 + 2010 combined	*P*-value	Correlation coefficient 2000–2010[b]
All	CBZ	121 (23%)	97 (15%)	0.002[a]	−0.94 (−0.99, −0.78)
	LEV	0 (0%)	49 (8%)	<0.001[a]	0.83 (0.48, 0.96)
	LTG	55 (10%)	150 (24%)	<0.001[a]	0.88 (0.59, 0.97)
	PHT	62 (12%)	31 (5%)	<0.001[a]	−0.83 (−0.95, −0.46)
	VPA	298 (56%)	307 (48%)	0.017	−0.64 (−0.90, −0.07)
	FOL	23 (4%)	51 (8%)	0.012	0.48 (−0.14, 0.84)
Children (<18 years)	FOL	3 (2%)	10 (5%)	0.169	0.34 (−0.32, 0.78)
Boys (<18 years)	CBZ	11 (13%)	11 (12%)	1.000	−0.10 (0.66, 0.53)
	LEV	0 (0%)	6 (6%)	0.049	0.66 (0.10, 0.90)
	LTG	9 (10%)	6 (6%)	0.471	0.07 (−0.56, 0.64)
	VPA	66 (77%)	71 (76%)	0.988	−0.37 (−0.78, 0.28)
Girls (<18 years)	CBZ	10 (15%)	9 (9%)	0.395	−0.58 (−0.87, 0.03)
	LEV	0 (0%)	9 (9%)	0.026	0.66 (0.09, 0.90)
	LTG	7 (11%)	33 (35%)	<0.001[a]	0.82 (0.44, 0.95)
	VPA	49 (74%)	44 (46%)	<0.001[a]	−0.76 (−0.93, −0.29)
Women (14–45 years)	CBZ	28 (26%)	16 (14%)	0.042	−0.64 (−0.89, −0.06)
	LEV	0 (0%)	14 (13%)	<0.001[a]	0.79 (0.37, 0.94)
	LTG	26 (25%)	51 (46%)	0.002[a]	0.84 (0.48, 0.96)
	PHT	4 (4%)	3 (3%)	0.951	−0.25 (−0.74, 0.41)
	VPA	48 (45%)	27 (24%)	0.001[a]	−0.87 (0.97, −0.57)
	FOL	14 (13%)	31 (28%)	0.062	0.51 (−0.12, 0.85)
Men (14–45 years)	CBZ	34 (32%)	23 (17%)	0.014	−0.80 (−0.94, −0.38)
	LEV	0 (0%)	12 (9%)	0.004	0.86 (0.54, 0.96)
	LTG	12 (11%)	37 (28%)	0.003	0.74 (0.26, 0.93)
	PHT	8 (7%)	4 (3%)	0.200	−0.56 (−0.86, 0.05)
	VPA	53 (50%)	57 (43%)	0.367	−0.15 (−0.69, 0.50)
	FOL	0 (0%)	3 (2%)	0.310	0.22 (−0.43, 0.73)

CBZ, carbamazepine; FOL, folic acid; LTG, lamotrigine; LEV, levetiracetam; PHT, phenytoin; VPA, sodium valproate; *p*-value for difference in proportions of the drug prescribed between the years 2010 and 2000.
[a] Significance at 95% level after Bonferonni correction for multiple testing.
[b] Pearson correlation coefficient over the 11 years with (95% confidence intervals).

and folic acid prescription over a 10-year timeline. Table 1 compares AEDs prescribed in 2000 and 2001 to those prescribed in 2009 and 2010, subdivided into age groups.

460 people were co-prescribed folic acid with their first AED. The mean proportion of people co-prescribed folic acid with their first AED between 2000 and 2010 was 6.2% (of all people); 20.3% (women 14–45 years); 3.2% (everyone except women 14–45 years); 1.5% (men 14–45 years); 3.6% (children aged 0–17 years); 3.8% (adults > 45 years). There was a significant difference in the proportion of folic acid co-prescribed to women aged 14–45 years when compared to all other patients (p-value < 0.001). There was no significant change over time in the proportion of folic acid prescribed to the cohort as a whole or to any of the sub-groups.

4. Discussion

We have demonstrated changes in the choice of first AED for new onset epilepsy between 2000 and 2010 in Wales. There was a trend for more prescriptions of lamotrigine and levetiracetam and fewer prescriptions of phenytoin and carbamazepine as a first AED. The increased use of lamotrigine may reflect better tolerability with similar efficacy when compared to carbamazepine in patients with focal seizures.[2] Levetiracetam's increasing use as a first choice AED since its introduction in the UK in 2000 can be explained by its efficacy in the treatment of generalised and focal epilepsies and its low rate of drug interactions, when compared with other AEDs.

Sodium valproate taken in pregnancy is associated with an increased rate of major congenital malformations (MCMs).[3] There is also increasing evidence that sodium valproate exposure during pregnancy is associated with a decrease in cognitive abilities in early childhood.[4] Lamotrigine and levetiracetam are associated with significantly lower rates of MCMs.[3,8] Prescribers' knowledge of this could explain our observation that women of childbearing age and girls are prescribed significantly less sodium valproate as a first-line AED and correspondingly more lamotrigine and levetiracetam.

It is well established that periconceptual folic acid supplementation reduces the risk of neural tube defects in the general population. However, the current UK national guidelines stating that women with epilepsy on AEDs who may become pregnant should receive folic acid, are based on a lower level of evidence.[5] To our knowledge, there were no publications during the study period producing positive evidence for folic acid supplementation during pregnancy in women with epilepsy. Indeed one study found no advantage in taking preconceptual folic acid.[9] This may explain why we did not see a significant change in the co-prescription of folic acid. This may now change, as patients and doctors become increasingly aware of evidence showing that maternal periconceptual folic acid may positively influence cognitive abilities in early childhood.[4]

It was not possible to record epilepsy type in this study; thus, some of the changing prescribing trends may have been due to a change in diagnosis of epilepsy syndrome. Folic acid is available "over the counter" and so some women may be taking folic acid even though they are not receiving a prescription from their GP. We have not captured AED prescriptions issued in hospitals in this study, however, this is likely to be a small proportion of total AED prescriptions in Wales. We have not distinguished between women aged 14 and 45 years who may or may not become pregnant – knowing that a woman of childbearing age is definitely not going to get pregnant can influence AED choice.

Two UK based studies looking at AED use in children and adults showed similar trends for increasing lamotrigine and

levetiracetam and decreasing valproate and phenytoin use, particularly in women.[10,11] An Australian study looking at AED use between 2003 and 2008 showed the same trends, apart from increasing use of sodium valproate.[12] To our knowledge, this is the first study to analyse specifically the trends of first time prescription of AEDs and concurrent folic acid prescription in the last decade.

In conclusion, we identified a change in the first AED prescribed for epilepsy in Wales between 2000 and 2010. There was significantly more lamotrigine and levetiracetam prescribed and significantly less sodium valproate prescribed to women of childbearing age and girls. The number of women co-prescribed folic acid did not change significantly during this time. These changing prescribing trends, particularly in women of childbearing age, are reassuring given that they reflect published evidence in terms of AED efficacy, tolerability and safety.

Contributions

WOP designed the study, analysed the data and wrote the first draft of the paper. ASL wrote and executed the database queries and assisted in study design and data analysis. RHT assisted with study design and edited the paper. PEMS and MIR supervised the project. MIR, PEMS, and RAL provided the research environment and edited the paper.

Competing interests

WOP and RHT previously received unrestricted grants from UCB Pharma for clinical research fellow salaries. PEMS and MIR obtained the above unrestricted UCB grants for clinical fellows salary through WERN.

All authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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