Article Title: Weight change associated with anti-epileptic drugs

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Key Words: Anticonvulsants, Anti-epileptic drugs, Adverse Effects, Body weight,

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 and edited the paper.

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Word Count :

ABSTRACT

Aim: To investigate anti-epileptic drug (AED) related weight changes in patients with epilepsy using a retrospective observational study.

Method: We analysed the anonymised electronic primary care records of 1.1 million adult patients in Wales. We included adult patients with a diagnosis of epilepsy, whose body weight had been measured up to 12 months before starting, and between 3 and 12 months after starting one of five AEDs. We calculated the weight difference after starting the AED for each patient.

Results: 1 423 patients were identified in total. The mean difference between body weight after and before starting each AED (together with 95% confidence intervals and p-values for no difference) were: carbamazepine 0.43 (-0.19, 1.05) p=0.17; lamotrigine 0.31 (-0.38, 1.00) p=0.38; levetiracetam 1.00 (0.16, 1.84) p=0.02; sodium valproate 0.74 (0.10, 1.38) p=0.02; topiramate -2.30 (-4.27, -0.33) p=0.02

Conclusions: Levetiracetam and sodium valproate were associated with significant weight gain, topiramate was associated with significant weight loss, and lamotrigine and carbamazepine were not associated with significant weight change.

INTRODUCTION

Around 600 000 people (approximately 1% of the UK population) have a diagnosis of epilepsy and are prescribed anti-epileptic drugs (AEDs).[1] Most of these people will need lifelong treatment with AEDs. It is important for clinicians to have an accurate understanding of the side effect profile of AEDs in order to select the most suitable AED and be able to provide appropriate information to the patient. Both clinicians and patients identify AED side effects as a priority area of research in epilepsy.[2]

There are several reasons why patients with epilepsy may experience weight change, one of these being AED therapy.[3] Weight gain is associated with an increased risk of co-morbidities (e.g. hypertension, type 2 diabetes mellitus, heart disease and some types of cancer) and impairs quality of life and self-esteem. Weight loss is also associated with co-morbidity (e.g. osteoporosis, immune and metabolic problems) - of particular importance in the young and elderly populations. Several AEDs have previously been linked to both weight

gain and weight loss.[3] If the risks of weight change are not adequately explained to patients then: they may lose the opportunity to ameliorate the risk via prospectively monitoring their weight and executing early lifestyle change; subsequent weight change may contribute to discontinuation of the associated AED with the associated risk of increased seizure frequency or the physician may risk stopping another medication not implicated in weight change by failing to identify the most likely drug.

Most of the limited literature currently available on weight change and AEDs is derived from data from clinical trials. Our aim was to investigate and quantify weight change associated with five of the most commonly prescribed AEDs in the UK in a primary care setting. Having been routinely collected in the community, these prospectively acquired data are free from pharmaceutical industry bias.

METHOD

General practice (GP) electronic health records are stored at the health information research unit (HIRU) at Swansea University as part of the secure anonymised information linkage (SAIL) system.[4,5] At the time of analysis, approximately 40% of the Welsh population's GP records were available on the SAIL system (around 1.1 million people).

We electronically searched all SAIL records for adult patients with a coded diagnosis of epilepsy (Read code F25). We then refined our search by including only those people who:

- had their weight recorded up to 12 months before starting one of five AEDs [carbamazepine (CBZ); lamotrigine (LTG); levetiracetam (LEV); sodium valproate (VPA) and topiramate (TPM)] for the first time as monotherapy *and*
- had their weight recorded within 3 to 12 months of starting and remaining on the same AED *and*
- were 18 years of age or older at the time of starting the AED. (Significant weight gain can occur during various stages of child development and so children were not included in this study).

We considered that most weight change associated with AED treatment occurs during the first 3 months after initiation,[6] and most people have reached an initial target dose in this period and so we chose a time window of 3–12 months after starting the AED for the second

weight measurement. We included generic and all recognised trade names for AEDs in the search. We excluded people who had a biologically implausible change (>40% of their baseline body weight) weight gain or loss within the study period.

For each patient meeting the above criteria, we recorded age, sex, weight before starting the AED and weight after starting the AED. We recorded whether each patient was on AED monotherapy, was co-prescribed a common drug which may affect weight (corticosteroids, hypoglycaemic agents, antidepressants or antipsychotics) or had a common comorbidity which may affect weight (diabetes, thyroid disease, depression, psychosis). We then calculated the time between the weight measurements and the weight difference (the difference between the weights measured before and after starting the AED) for each person. We checked that the distribution of the absolute and relative weight changes were approximately normally distributed by plotting frequency and normal plots. Using paired t-tests, we calculated the significance levels and confidence limits for the mean weight difference and mean percentage weight difference for each drug group. We used χ^2 tests to compare the proportions of each group on AED monotherapy, co-prescribed common drugs which may cause weight change or with common potentially weight changing co-morbidities.

This project was approved by the HIRU information governance panel (project 0193). The National Research Ethics Service (NRES) has confirmed that projects using the anonymised data held by HIRU do not need specific NHS research ethics committee approval.

RESULTS

We identified 19 622 adult patients with a diagnosis of epilepsy (approximately 1.5% of the population covered by the SAIL database). Of these, 1 423 patients met our inclusion criteria. These patients had their weights recorded between the 18/11/1988 and 04/04/2011. Table 1 and figure 1 gives the main results.

Drug	n	% male	Age / years ± 1 s.d.	Mean weight before / kg ± 1 s.d.	% on AED monotherapy (95% c.i.)[a]	% on other medication potentially causing weight change (95% c.i.)[b]	% with co-morbidities potentially causing weight change (95% c.i)[b]	Mean weight change / kg (95% c.i.) p-value[c]	Mean % weight change (95% c.i.) p-value[c]
CBZ	362	47	50.3 ± 18.1	79.2 ± 19.5	61.4 (56.4,66.3)	20.1 (16.0,24.2)	20.9 (16.8,25.0)	0.43 (-0.19,1.05) p=0.17	0.74 (-0.07,1.55) p=0.07
LTG	297	34	44.3 ± 18.8	76.6 ± 19.8	79.8 (75.3,84.2)	18.3 (14.0,22.6)	19.9 (15.5,24.2)	0.31 (-0.38, 1.00) p=0.38	0.50 (-0.41, 1.41) p=0.28
LEV	201	42	45.2 ± 16.3	80.3 ± 21.8	76.3 (70.6,82.0)	15.6 (10.7,20.5)	17.1 (12.0,22.1)	**1.00** (0.16, 1.84) **p=0.02**	**1.61** (0.44, 2.78) **p=0.007**
VPA	496	50	50.7 ± 19.7	78.7 ± 20.4	72.4 (68.6,76.2)	17.9 (14.6,21.2)	21.0 (17.7,24.6)	**0.74** (0.10, 1.38) **p=0.02**	**1.21** (0.41, 2.01) **p=0.003**
TPM	67	27	40.4 ± 13.2	86.5 ± 24.8	65.7 (54.5,76.8)	17.1 (8.3, 26.0)	17.1 (8.3,26.0)	**-2.30** (-4.27, -0.33) **p=0.02**	**-2.62** (-4.60, -0.64) **p=0.01**

Table 1 : Results (CBZ = carbamazepine; LTG = lamotrigine; LEV = levetiracetam; VPA = sodium valproate; TPM = topiramate; s.d. = standard deviation; c.i. = confidence interval) [a]p-value <0.05 using χ^2 test (4 dof), null hypothesis no difference between groups [b] p-value >0.05 using χ^2 test (4 dof), null hypothesis no difference between groups ; [c]p-value using paired t-test and the null hypothesis of no weight change)

<< Insert Figure 1 here >>

Although broadly similar, there were some differences between groups in terms of patient demographics. There were significantly fewer patients in the topiramate group (n=67) compared with the other patient groups. Each patient group had 50% or more women, with LTG (66%) and TPM (73%) in particular having the highest proportion of women. The CBZ and VPA groups had a slightly older mean age in years (± 1sd) of 50.3 (± 18.1) and 50.7 (± 19.7). The TPM group had a younger mean age of 40.4 (± 13.2). The time between the weight measurements was similar for all drug groups. The mean time in days between the first weight measurement and starting the AED was CBZ 119; LTG 119; LEV 127; VPA 125 and TPM 119. The mean time in days between the second weight measurement and starting the AED was CBZ 208; LTG 200; LEV 193; VPA 211 and TPM 203.

Excessive weight changes are more important for the individual and can lead to discontinuing AED therapy. The proportion of people with a weight **gain** of > 10% (95% c.i.) for each drug group were CBZ 7.5% (4.6%, 10.3%); LTG 6.0% (3.2%, 8.9%); LEV 10.0% (5.6,

14.3); VPA 11.9% (8.9, 14.8) and TPM 4.5% (0, 10.2%). The proportion of people with a weight **loss** of > 10% (95% c.i.) for each drug group were CBZ 7.7% (4.8%, 10.6%); LTG 3.7% (1.4%, 6.0%); LEV 4.0% (1.0%, 6.9%); VPA 5.8% (3.7%, 8.0%); TPM 13.4% (4.5%, 22.3%).

DISCUSSION

Our data show that patients taking topiramate had a significant absolute and relative weight loss and that the levetiracetam and sodium valproate groups had significant absolute and relative mean weight gain. Patients taking carbamazepine and lamotrigine had non-significant absolute and relative mean weight gain. We believe that this is the first study to demonstrate significant weight gain with levetiracetam.

There was no significant difference between the groups in terms of the proportion of patients losing or gaining more than 10% of their baseline weight, or co-prescribed common drugs and common comorbidities known to cause weight change. The carbamazepine group had a significantly lower number of people on AED monotherapy when compared with the lamotrigine, levetiracetam and sodium valproate groups.

There are inherent biases with this retrospective observational study. In particular, only patients who had their weight measured during a GP consultation within the appropriate time period were included. Patients who did not visit their GP or visited their GP but did not get their weight recorded were not included. However, this bias applies equally to each drug group in this study. The demographics of each group are also slightly different and may account for some of the differences in weight change between the groups; however this would not explain the difference in weight changes between the lamotrigine and levetiracetam group who are not significantly different in terms of age, sex or baseline weight.

Previous data, largely from clinical trials, have associated weight gain with sodium valproate[3,7] and weight loss with topiramate.[8] Lamotrigine is generally considered to be weight neutral.[9] Both weight gain[10,11] and weight neutrality[12] has been associated with carbamazepine.

A study by Gidal *et al* using pooled data from four clinical trials showed that levetiracetam did not cause weight gain[13]. It is not entirely clear why this finding is not replicated in our

study although the patients in the Gidel *et al* study were monitored regularly as part of clinical trials as opposed to being followed up in the community and were already established on one or two AEDs before starting levetiracetam (76% of our patients were on levetiracetam monotherapy).

There are several mechanisms which may explain how sodium valproate causes weight gain, these include dysregulation of hypothalamic weight regulation mechanisms; altered adipokine (adipose tissue cytokine) transmission and altered insulin secretion / resistance.[6] Levetiracetam has a different mode of action than sodium valproate and the function of its main molecular target, synaptic vesicle protein 2A (SV2A) is largely unknown,[16] however, it may have a role in similar weight changing pathways.

Topiramate is not normally used as a first line treatment for epilepsy – it is therefore less commonly prescribed than other AEDs explaining the fewer patients in the topiramate group. Epilepsy is considered to be slightly more common in males than females.[14] The larger number of female patients in this study may be explained by the fact that women are more likely to visit their general practitioner,[15] and may be more likely to consult about weight changes than men. Sodium valproate and carbamazepine are the oldest drugs in the group reflected in the slightly older mean age of the patients taking these drugs.

In conclusion, when patients with epilepsy are observed in a primary care setting, certain antiepileptic drugs are associated with weight change. Levetiracetam and sodium valproate are associated with significant weight gain, topiramate with significant weight loss. Carbamazepine and lamotrigine are not associated with significant weight gain. We believe that this is the first time that levetiracetam has been associated with weight gain in a cohort of patients. Patients and clinicians need to be aware of the potential for weight change when starting AED therapy.

ACKNOWLEDGEMENTS

This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales. We would like to acknowledge all the data providers who make anonymised data available for research. (HIRU project number 0193). The Wales Epilepsy Research Network

(WERN) provided the infrastructure and resources for this project. Thanks to C H Roberts for proofreading the text.

COMPETING INTERESTS

WOP receives an unrestricted grant from UCB Pharma for his clinical research fellow salary. RHT has previously received an unrestricted grant from UCB Pharma for a clinical research fellow salary. PEMS and MIR obtained the above unrestricted UCB grant for clinical fellows salary through WERN.

FUNDING

WERN is funded by the Welsh Government through the National Institute for Social Care and Health Research (NISCHR).

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