

## PAPER

# The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies

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**Objective:** To examine a large population with idiopathic generalised epilepsy (IGE), and estimate the overall remission rates for the IGEs and subsyndromes in a clinic based sample. Remission rates on valproate, lamotrigine, topiramate, and combinations of these antiepileptic drugs were estimated and factors predicting outcome examined.

**Methods:** All patients with IGE were identified from a computerised database and EEG records at large adult and paediatric epilepsy clinics. Data were recorded retrospectively on demographics and clinical information, seizure types and syndrome diagnosis, antiepileptic drug treatment details, and remission rates.

**Results:** 54.3% of 962 patients had achieved a one year period of remission; this was most likely with valproate monotherapy (52.1%), with lower rates for lamotrigine and topiramate (16.7% and 34.6%, respectively). The combination of valproate and lamotrigine achieved a remission rate of 15.3%. The factor most predictive of a response to a particular antiepileptic drug regimen was the rank order in which it was given. Relapse rate was high (79.9%) after antiepileptic drug withdrawal in remission, particularly with juvenile myoclonic epilepsy (93.6%).

**Conclusions:** Valproate may be the most effective antiepileptic drug in the treatment of the IGEs. Combination therapy should be initiated if an adequate trial of valproate monotherapy is not effective, rather than switching to alternative monotherapy. Antiepileptic drug treatment needs to be lifelong in many adult patients with IGE.

Although the idiopathic generalised epilepsies (IGEs) generally present in childhood and adolescence, they account for up to 30% of all patients attending adult epilepsy clinics. There is some degree of heterogeneity within the diagnostic group, but there is generally a good response to appropriate antiepileptic drug treatment, and particularly high rates may be seen with valproate.<sup>1,2</sup> However, there is still a subgroup of 20–30% of patients who remain refractory to treatment.<sup>2</sup>

Randomised controlled clinical trials are the gold standard in determining the efficacy and tolerability of an antiepileptic drug. Generally, randomised controlled trials of the drug treatment of epilepsy have compared an antiepileptic drug with a placebo and not with other antiepileptic drugs. Comparative trials are particularly rare in the IGEs.<sup>3–5</sup> There have been few randomised controlled trials in patients with IGE, partly because the response to valproate is so good, but also because of difficulties in recruiting children and adolescents into clinical trials. Some comparative studies in newly diagnosed populations have recruited patients with IGE, but subgroups are difficult to identify within these studies. Meta-analyses can provide data on larger patient numbers, but a meta-analysis of trials of carbamazepine versus valproate monotherapy highlighted the problem of misclassification of epilepsy syndromes within clinical trials which makes conclusions about the superiority of valproate questionable.<sup>6</sup>

There are therefore few data other than those derived from clinical experience to guide us in the treatment of our patients with IGE. In spite of this, it is generally accepted that valproate is the drug of choice for the treatment of the IGEs, as this has proven efficacy in all generalised seizure types.<sup>7</sup> However, there are some concerns over the potential adverse effects of valproate, particularly in women of child bearing age.<sup>8–12</sup> There are animal and clinical trial data on the efficacy

of the newer antiepileptic drugs lamotrigine and topiramate in the IGEs.<sup>13–16</sup> Based on current data we are unable to determine whether the newer drugs offer any advantages over valproate in terms of their tolerability and efficacy in patients refractory to valproate, or whether there are specific subgroups of patients in whom we should be targeting the newer antiepileptic drugs as a first line treatment.

Our aim in this study was to examine a group of patients with IGE, estimate the overall remission rates for the IGEs and specific epilepsy syndromes, and determine the remission rates on valproate, lamotrigine, topiramate, and combinations of these drugs. We also wanted to identify factors predictive of outcome and explore whether the probability of remission of epilepsy over time is similar for IGE and partial epilepsy.<sup>17</sup>

## METHODS

Data from the patients attending the Mersey regional epilepsy clinic have been computerised since 1989, with demographic data as well as diagnostic and treatment details. Patients with IGE were identified from this database at the Walton Centre. At a satellite clinic (run by DS) the patients were identified from a manually recorded patient data file. Children were identified by searching diagnostic coding from clinic letters and EEG requests. An epilepsy syndrome diagnosis was made for each patient, based on the clinical

**Abbreviations:** CAE, childhood absence epilepsy; GTCA, generalised tonic-clonic seizures on awakening; IGE, idiopathic generalised epilepsy; ILAE, International League Against Epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy

**Table 1** Frequency of each IGE subsyndrome in the study population

Type of epilepsy	n (%)
<i>Absence epilepsies (n = 288)</i>	
Childhood absence epilepsy	127 (13.2%)
Juvenile absence epilepsy	108 (11.2%)
Idiopathic absence epilepsy	46 (4.8%)
Eyelid myoclonia with absences	7 (0.7%)
<i>Myoclonic epilepsies (n = 424)</i>	
Juvenile myoclonic epilepsy	357 (37.1%)
Idiopathic myoclonic epilepsy	31 (3.2%)
CAE evolving to JME	25 (2.6%)
JAE/JME overlap	8 (0.8%)
Benign myoclonic epilepsy of infancy	3 (0.3%)
<i>Other syndromes (n = 250)</i>	
Tonic-clonic seizures on awakening	54 (6%)
Tonic-clonic seizures only	189 (19.6%)
Pure photosensitive epilepsy	7 (0.7%)
<b>Total</b>	<b>962</b>

CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy.

and EEG features according to the ILAE classification where possible,<sup>18</sup> but in order to encompass a wider range of clinical descriptions other diagnoses or subsyndromes were included: childhood absence epilepsy (CAE) evolving to juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE)/JME overlap, idiopathic absence or myoclonic epilepsy (where a definite diagnosis of an absence or myoclonic IGE did not conform with a recognised subsyndrome), and eyelid myoclonia with absences.

The case notes of all patients identified were searched. For inclusion into the study the following had to be satisfied:

- the clinical criteria for the diagnosis of IGE were fulfilled from review of the case notes, even if there was no EEG confirmation of generalised spike-wave;
- patients outside the normal age of onset for IGE (under 2 or over 26 years) were included if it was felt that the diagnosis was secure. Patients were excluded if these criteria were not satisfied, or if the basic data were not available from the case notes.

The following data were recorded from the case notes for each patient: basic demographics, family history of epilepsy in a first degree relative, history of febrile convulsions, seizure types and dates of onset, EEG results, antiepileptic drug treatment history, and longest seizure-free period on each antiepileptic drug regimen.

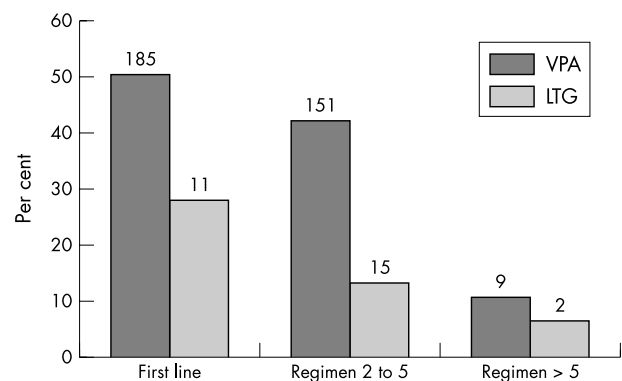
## RESULTS

In all, 962 patients with IGE were identified in the three centres (408 male and 554 female). Of these, 117 were

identified from the paediatric clinic. Table 1 summarises the frequency of the IGE subsyndromes within this population. There was a family history of epilepsy in a first degree relative in 216 patients (22.5%), and previous febrile convulsions in 105 (10.9%). EEGs were available in 902 patients, with generalised spike-wave noted in 613 (68%). In all, 257 patients (28.5%) had a photoparoxysmal response; this was most common in JME (31.9%) and isolated tonic-clonic seizures (32.6%) and least common in CAE and generalised tonic-clonic seizures on awakening (GTCA) (19.2% and 20%, respectively).

Complete antiepileptic drug data were obtainable in 787 patients, with information on periods of remission in all the others. Of the 899 who had been diagnosed for more than one year, 488 (54.3%) had achieved a one year remission at any time. This was most commonly achieved with valproate monotherapy (52.1%), and lower frequencies were observed with lamotrigine and topiramate monotherapy (16.7% and 34.6%, respectively). The most commonly used antiepileptic drug combination was valproate and lamotrigine, which achieved remission in 15.3% of the patients (table 2). There were 334 patients (37.2%) who had been in remission for the previous 12 months at the last follow up.

When treatment with valproate failed and it was substituted by lamotrigine (in patients who had not previously received lamotrigine), six of 44 patients (13.6%) achieved remission. This only occurred in patients who had failed valproate because of side effects, whereas in those in whom valproate was ineffective in controlling seizures, none achieved remission. When lamotrigine was added to valproate, 10 of 83 patients (12%) achieved remission, irrespective of the reason for valproate failure. In the reverse situation (add or switch to valproate after lamotrigine failure), the numbers were very small, but three of six achieved remission on switching to valproate.



**Figure 1** Remission rate depending on rank order in which valproate or lamotrigine monotherapy was given.

**Table 2** Remission rates achieved at any time during follow up with each antiepileptic drug regimen

Regime	n	Remission, 1 y	Remission, 2 y	Remission, 5 y
<i>Monotherapy</i>				
Valproate (VPA)	549	286 (52.1%)	226 (41.2%)	49 (8.9%)
Lamotrigine (LTG)	156	26 (16.7%)	12 (7.7%)	1 (0.6%)
Topiramate (TPM)	26	9 (34.6%)	3 (11.5%)	0 (0%)
<i>Combination treatments</i>				
VPA/LTG	157	24 (15.3%)	13 (8.3%)	2 (1.3%)
VPA/TPM	40	2 (5.0%)	1 (2.5%)	0 (0%)
LTG/TPM	21	3 (14.3%)	2 (9.5%)	1 (4.8%)

Mean daily dose of monotherapy: valproate 1286 mg, lamotrigine 324 mg, topiramate 256 mg. y, year.

The success of each antiepileptic drug was also dependent on the order in which the drug was given. Each drug was most likely to induce remission when given as first treatment, as compared with regimens two to five, or more than five regimens (fig 1). The outcome was independent of where treatment was initiated, with remission at any time occurring in 51.4% of patients diagnosed at a study centre (114 of 222) compared with 55.4% (375 of 677) diagnosed elsewhere. However, there was a difference in the initial antiepileptic drug used depending on where this was started. Almost 90% of patients who started treatment at one of the study centres began on valproate or lamotrigine. This was only the case in 60% of patients diagnosed outside the study centres, with carbamazepine being used in 30%.

Factors predictive of prognosis were assessed (table 3). Patients with generalised tonic-clonic seizures on awakening and tonic-clonic seizures only (odds ratios (OR) 3.16 and 1.62, respectively) had the best outcome. The factors most predictive of a poor outcome were an age of onset less than five years (OR, 0.72), or an "atypical" presentation. In typical cases, the remission rate with monotherapy was 48.3% (262 of 543) for valproate, and 14.4% (24 of 167) for lamotrigine. In atypical cases this was reduced to 37.5% (39 of 104) and 11.6% (5 of 43), respectively.

One hundred and sixty four patients attempted antiepileptic drug withdrawal when in remission, and relapse occurred in 131 (79.9%). There was at least a six months follow up in all patients following antiepileptic drug withdrawal. Eighty four of these (51.2%) were in remission at the time of writing (42 (25.6%) off antiepileptic drugs). Relapse was most common in patients with JME (44 of 47 (93.6%)), and least common in CAE (19 of 29 (65.5%)) and JAE (13 of 19 (68.4%)).

## DISCUSSION

There are limitations to this study. There may be unquantifiable bias in the ways in which treatments were selected for the patients. The retrospective design within specialist centres

means that subgroups with particularly good outcomes may be underrepresented, but every attempt has been made to ensure the data are as complete as possible by using a computerised database and case records from the centre, as well as other hospitals where necessary. Patients were included without the typical EEG abnormality of generalised spike-wave pattern if the clinical diagnosis (based on seizure semiology and demographics) was secure. If there was any doubt over the diagnosis on clinical grounds, the patient was excluded, thereby minimising the inclusion of those without IGE. This approach keeps the study relevant to clinical practice.

The remission rate was lower in this population than usually described for the IGEs.<sup>2</sup> This is to be expected as the majority of the patients were from an adult epilepsy clinic and so by their very nature had IGE that had persisted into adult life. In addition, the paediatric patients were attending a specialist paediatric neurology clinic and could arguably be expected to have relatively more refractory epilepsy. It is possible that the overall remission rates are an underestimate, as a proportion of those lost to follow may have had well controlled epilepsy. It should also be remembered that this is a selected population that is likely to represent the most severe cases. This study therefore does not give an indication of prognosis in the IGE population as a whole but does show that there are significant numbers of patients with IGE who remain refractory to antiepileptic drug treatment.

Antiepileptic drug regimens containing drugs other than valproate, lamotrigine, and topiramate have often been used in this population. Such regimens have involved appropriate antiepileptic drugs for specific seizure types (such as ethosuximide and the benzodiazepines), older drugs (for example, phenobarbitone), or inappropriate drugs when the syndrome was not initially recognised as IGE. This misdiagnosis was less common in the specialist centres, but the overall remission rates were similar when appropriate antiepileptic drug treatment was initiated, suggesting similar clinical features between the two groups.

**Table 3** Factors affecting prognosis of IGE (univariate analysis)

Variable	No of patients	No achieving remission*	OR (95% CI)
Sex			
Male	380	209	(55.0) 1.0
Female	519	279	(53.8) 0.95 (0.72 to 1.25)
Age of onset (years)			
<5	60	28	(46.7) 0.72 (0.41 to 1.26)
5–10	231	117	(50.6) 0.82 (0.60 to 1.12)
10–20	546	308	(56.4) 1.24 (0.94 to 1.64)
>20	62	35	(56.5) 1.10 (0.63 to 1.92)
EEG			
GSW	575	302	(52.5) 0.83 (0.62 to 1.10)
Photic	233	131	(56.2) 1.11 (0.82 to 1.52)
Focal	98	61	(62.2) 1.44 (0.92 to 2.29)
Syndrome			
CAE	122	64	(52.5) 0.90 (0.60 to 1.34)
JAE	98	55	(56.1) 1.07 (0.69 to 1.67)
JME	341	170	(49.9) 0.75 (0.57 to 0.99)
GTCA	50	39	(78.0) 3.16 (1.56 to 6.93)†
TC only	169	109	(64.5) 1.68 (1.17 to 2.42)‡
"Typical" IGE**	745	417	(56.0) 1.47 (1.02 to 2.12)§
"Atypical" IGE**	139	64	(46.0) 0.68 (0.46 to 0.99)¶
Febrile convulsions	99	59	(59.6) 1.28 (0.82 to 2.00)
Family history of epilepsy	207	104	(50.2) 0.81 (0.57 to 1.12)

\*Values are number (%) achieving remission, odds ratios, and 95% confidence intervals.

\*\*"Typical IGE" defined as CAE, JAE, JME, or a syndrome of tonic-clonic seizures only with an age of onset >3 years and <20 years; "atypical" IGE includes patients with atypical absence and myoclonic epilepsies, and tonic-clonic seizures only, outside of the specified age of onset.

†p=0.0006; ‡p=0.004; §p=0.03; ¶p=0.04.

CAE, childhood absence epilepsy; CI, confidence interval; GSW, generalised spike wave; GTCA, generalised tonic-clonic seizures on awakening; IGE, idiopathic generalised epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; OR, odds ratio; TC, tonic-clonic seizures.

One of the most significant factors in assessing the effect of an antiepileptic drug in the IGEs appears to be the rank order in which a drug is given. Each of the drugs assessed was more likely to be successful the earlier in the treatment regimen it was given (fig 1). This is in concordance with previous work on the overall prognosis of epilepsy in studies consisting largely of patients with partial epilepsy.<sup>17</sup> This is the first time this has been shown in a study exclusively dealing with patients with IGE.

A factor predictive of a poor outcome was age at onset less than five years. These children have predominantly been classified as either "idiopathic absence" or "idiopathic myoclonic" epilepsies, as they do not fit into the conventional classification. It may be that patients with a younger age of onset of absence or myoclonic epilepsies and without any cognitive decline, and who otherwise conform to a clinical diagnosis of IGE, represent a genotypic variant with a poorer prognosis. This group also includes some patients with less common syndromes that are known to have a worse prognosis, such as eyelid myoclonia with absences.<sup>19</sup> If patients with "typical" IGE are the only ones included in this analysis (age of onset over three years), then the remission rate was higher, at 62.5% (15 of 24; odds ratio, 1.42 (95% confidence interval, 0.57 to 3.7)). A worse prognosis overall for patients who did not have typical syndromic diagnoses was also found.

The overall outcome in the absence epilepsies was worse than one would expect in a population with this diagnosis. This may in part be a reflection of the proportion of adults in the study in whom the epilepsy had persisted from childhood. The syndrome of tonic-clonic seizures on awakening had an excellent prognosis, which is supported by previous studies.<sup>1</sup>

The conventional antiepileptic drug of choice for the treatment of the IGEs is valproate. However, with the introduction of newer drugs such as lamotrigine and topiramate the treatment options are greater at a time when there are increasing concerns over the side effect profile and teratogenicity of valproate. As a result, lamotrigine is now commonly advocated for the treatment of the IGEs in women. There are no comparative studies to show whether these newer drugs are as effective as valproate in the IGEs, or whether they offer any advantages in terms of tolerability. Our study provides some evidence that lamotrigine may not be as effective as valproate in this condition. Although not directly comparable owing to the duration of epilepsy and a potential selection bias, the remission rate of 16.7% for lamotrigine is low when compared with the 52.1% for valproate. It is well recognised that response to the first antiepileptic drug is an important predictor of outcome,<sup>20</sup> but even when only the drug given as first treatment was

considered, the results differed greatly between lamotrigine and valproate (fig 1), although the numbers in the lamotrigine group were relatively small. The differences between the two groups could also influence the response to a particular drug. Patients with CAE were less likely to receive lamotrigine as first line treatment than valproate, although the use of the two drugs in the absence epilepsies was similar overall (table 4). Also, women were more likely to receive lamotrigine as first line treatment, although this is unlikely to have affected the outcome (tables 3 and 4). The analysis of the outcome of adding or switching over to lamotrigine from valproate is consistent with lamotrigine being less effective. We conclude that when valproate fails because of lack of efficacy, switchover to lamotrigine is unlikely to be successful and in this situation a second antiepileptic drug should be added. If, however, valproate fails because of adverse effects then switching to an alternative antiepileptic drug is appropriate.

Topiramate appears to be a useful option with encouraging results, but the numbers are too small to draw meaningful conclusions. A commonly prescribed antiepileptic drug combination for IGE is valproate and lamotrigine, as there is some evidence of a synergistic effect.<sup>22-23</sup> The remission rate in this study of 15.3% is higher than usually expected with antiepileptic drug combinations<sup>24</sup> and provides further evidence for the efficacy of this specific combination.

A dilemma that faces both patients and physicians is the decision about whether to attempt antiepileptic drug withdrawal during remission. It is difficult to extrapolate data to the IGEs from previous studies that examined mostly patients with partial epilepsy. In our study the relapse rate following antiepileptic drug withdrawal was 79.9%, confirming the impression that many patients with IGE need lifelong treatment. This may even be an underestimate of the true relapse rate, as some patients may have had a relapse and not returned to the clinic. The syndromic diagnosis had a significant impact on relapse rate, and our findings confirm that remission off antiepileptic drugs is rare in JME.<sup>25</sup> The relapse rates in all IGE syndromes in this population are high, and this needs to be considered when counselling adults with IGE who are in remission and are considering treatment withdrawal.

## Conclusions

This is the first published study of such a large number of patients with IGE, and provides data on aspects of prognosis and treatment of this common but understudied form of epilepsy. The most important factor influencing outcome with a particular antiepileptic drug was the rank order in which it was given. Valproate may still be the most effective drug for the treatment of the IGEs, but individual patients may benefit from the other options available. Combination therapy should be initiated if an adequate trial of valproate monotherapy is not effective, rather than switching to an alternative monotherapy. Valproate with lamotrigine is a particularly useful combination when a single antiepileptic drug has failed. Relapse on attempted withdrawal of antiepileptic drugs was common in this population, particularly in patients with JME in whom antiepileptic drug treatment usually needs to be lifelong.

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**Table 4** Comparison of patient characteristics according to initial antiepileptic drug used

Factor	Valproate (n = 391)	Lamotrigine (n = 61)
Sex, F:M (% male)	211:180 (46.0)	45:16 (26.2)
Age of onset (years)*	12.2 (5.3)	14.1 (5.0)
Diagnosis		
CAE	52 (13.3%)	4 (6.6%)
JAE	45 (11.5%)	12 (20.0%)
JME	140 (35.8%)	19 (31.1%)
TC only	102 (26.1%)	20 (32.8%)
Others	52 (13.3%)	6 (9.8%)
Mean dose (mg)*	1115 (624)	271 (157)
Mean dose (%DDD)†	0.74	0.90

\*Mean (SD).

†DDD, defined daily dose: valproate = 1500 mg, lamotrigine = 300 mg.<sup>21</sup>

CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; TC, tonic-clonic.

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