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Seizures in Rett syndrome: an overview from a one-year calendar study

Le Jian^a, Lakshmi Nagarajan^b, Nicholas de Klerk^a, David Ravine^c, John Christodoulou^{d,e}, and Helen Leonard^{a,*}

^a Centre for Child Health Research, The University of Western Australia, Telethon Institute for Child Health Research, Perth, Western Australia

^b Department of Neurology, Princess Margaret Hospital for Children, Roberts Road, Subiaco, Perth, Western Australia

^c West Australian Institute of Medical Research and Centre for Medical Research, The University of Western Australia, Perth, Western Australia

^d School of Paediatrics and Child Health, University of Sydney, New South Wales

^e Western Sydney Genetics Program, Children's Hospital at Westmead, Sydney

SUMMARY

Background—Rett syndrome is a neurodevelopmental disorder mainly affecting females. It is principally caused by mutations in the *MECP2* gene. Seizures occur in about 80% of subjects but there has been little research into the factors contributing to their frequency.

Aims—To investigate seizure frequency in Rett syndrome and its relationship with other factors, including genetic characteristics and the use of anti-epileptic drugs.

Methods—Information on daily seizure occurrence and health service utilisation and monthly anti-epileptic drug use was provided on 162 Rett syndrome cases for a calendar year. Age at onset of seizures, developmental history and other clinical and genetic characteristics were obtained from a contemporaneously completed questionnaire and from the Australian Rett Syndrome Database. Negative binomial regression was used to investigate factors associated with seizure rates.

Results—Seizure rates were highest in the 7–12 year age group. They were lower in those with p.R294X, p.R255X mutations and C terminal mutations. Those who had early developmental problems and poorer mobility had higher seizure rates as did those with greater clinical severity and poorer functional ability. Many different combinations of medications were being used with carbamazepine, sodium valproate and lamotrigine either singly or in combination with another being the most common.

Conclusions—Seizure frequency in Rett syndrome is age-dependent, more common in those with more severe early developmental problems and influenced by mutation type.

*Corresponding author: Dr Helen Leonard, Telethon Institute for Child Health Research, PO Box 855, West Perth WA 6872, Tel: (08) 61 8 9489 7790, Fax: (08) 61 8 9489 7700, hleonard@ichr.uwa.edu.au.

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Keywords

Rett syndrome; Seizure rate; Epilepsy; *MECP2* mutations; Early development; Clinical severity; Anti-epileptic drugs

1. Introduction

Rett syndrome is a neurodevelopmental disorder mainly affecting females and caused principally by mutations in the *MECP2* gene.¹ Although the phenotype is generally severe, the clinical spectrum is variable with a number of associated comorbidities including reduced somatic growth, gastro-intestinal disease, osteopenia, autonomic dysfunction and scoliosis. Seizures, which have a considerable impact for those affected and their families occur in about 80% of subjects. The Australian Rett Syndrome Database (ARSD) has been using multiple sources to ascertain Rett syndrome cases in Australia among individuals born since 1976.² Information on functional, medical, educational and other aspects of the cohort have been collected every two years since 2000 through questionnaires completed by parents and carers. During 2000 families also completed a daily calendar in which they reported episodes of seizures, medical and other health appointments and hospitalizations experienced by the subjects.³ In this report we use these contemporaneously recorded data to determine seizure rates and to investigate their relationship with demographic, clinical, genetic and other factors. We also describe the range and combinations of anti-epileptic drugs (AEDs) being used by this Rett syndrome population.

2. Material and methods

2.1. Data sources

Families and caregivers of 162 verified female cases ascertained from the Australian Rett Syndrome Database (ARSD, www.ichr.uwa.edu.au/rett/aussierett/),⁴ participated in a year long calendar study in 2000 (CS2000).³ These cases represented 81.4% of the cases who were in the ARSD at that time. Over three quarters (78.4%) were classical according to the recently revised criteria⁵ compared with 67% in a more recent cohort.⁴ Families were asked to record, in a calendar format, and return on a monthly basis information, detailing daily events in seven categories: medical, health and therapy appointments; hospital stays; nursing care; seizure activity; and other health events. The reasons for each appointment and the type of doctor or health professional involved in were recorded. Details of all prescribed and non-prescribed medications were also recorded on a monthly basis. As well as completing the calendar, families also participated in a follow-up study in 2000 (FUS2000) the methodology for which has been previously described.² Information provided by families and caregivers, for example regarding mobility and the presence of health problems such as abnormal breathing and sleep disturbance as well as weight, height and head circumference measurements, was available for this analysis. Epilepsy diagnosis was based on the age at seizure onset as previously⁶ or if AEDs were being used for seizure control (n=4).

2.2. Severity scores

Several severity scores derived from the FUS2000 data² were also included in the current analysis. The modified WeeFIM is a composite score that increases to a maximum of 126 with increasing independent functioning.⁷ The Kerr score was developed from the system suggested as a guideline for reporting clinical severity in Rett syndrome,⁸ the Pineda score from the scaling system originally developed by Monros⁹ and the Percy score from the score modified by Schanen and Percy¹⁰ from Amir and Zoghbi.¹¹ In contrast to the WeeFIM, these numerical scores increase with increasing severity.

2.3. Mutation testing

MECP2 gene mutation testing has been completed in the majority of cases (154/162, 95.1%), with pathogenic mutations identified in 118 (72.6 %). Details of the methods employed for *MECP2* mutation testing have been previously described.⁶ X inactivation was categorized as skewed when one X-chromosome was active in 25% or less of all analyzed cells.¹²

2.4. Data management

To examine the relationship between parent-reported seizure activity and genetic findings, the cases were categorized into the following mutation types: p.R168X, p.T158M, p.R294X, p.R270X, p.R255X, p.R133C, p.R306C, p.R106W, large deletions involving exon 3 and 4, C-terminal deletions in exon 4, early truncating (truncations up to and including the nuclear localization signal (NLS) region within the transcription repression domain (TRD), except for p.R270X, p.R255X and p.R168X), and a final group that included all other pathogenic mutations. Separate categories were included for those in whom a *MECP2* mutation was sought but not identified and those who were not tested.

The z-score for head circumference (HC) in 2000 was calculated based on the following formula: (HC of child – reference mean HC)/reference standard deviation (SD) of HC. The reference mean and SD were obtained from a Dutch study which provided population norms.¹³ Z-scores for body mass index (BMI, kg/m²) were calculated using the formula and reference median values for females aged 2– 20 years provided by the Centre for Disease Control.¹⁴ The reference value for age 20 years was also applied to any individual over this age. HC z-score in 2000 and BMI z-score in 2000 were divided into three categories based on the distribution of the cases in this study: a reference group with z-scores ranging from 25th percentile (P₂₅) to 75th percentile (P₇₅), with the other two groups below P₂₅ and above P₇₅.

Information on the use of AEDs was collected from CS2000. Cases were classified as users of an AED if they used it for one or more months in the year. Combination(s) of AEDs used the same “no/yes” model. The AEDs were categorised as “old” drugs if they belonged to the first line AEDs according to the specifications of the Australian Pharmaceutical Benefits Scheme (PBS).¹⁵ The rest (lamotrigine, topiramate, clobazam, vigabatrin, gabapentin and tigabine) were categorised as “new” drugs. Cases using any new medication were coded as being on new medication irrespective of the continuation of the additional use of old medications. To investigate the relationship between parent-reported seizure episodes and the pattern of AED use, those on AEDs in 2000 were also divided into two groups according to whether they had changed their AEDs during that year. If the same medication was withdrawn but subsequently reinstated, the case was considered in the “no medication change” group.

2.5. Statistical analysis

If multiple seizures (n=31) but not the exact number (n=12) were reported we used the average for those who had provided the number of multiple seizures. Annual (and monthly) seizure rates were calculated by dividing the total number of seizures recorded during the year by the number of days of participation in the study. Because of the large dispersion in seizure rates, negative binomial regression was used to investigate the factors associated with seizure rates. Seizure rate ratios (RR) were used to estimate the associations of other variables with seizure rates. STATA version 9.0¹⁶ was used for analysis.

3. Results

One hundred and thirty eight of the 162 cases (85.2%) in CS2000 had been diagnosed with epilepsy (Table 1). The mean age of this group was 14.0 years (range 2.3–24.6), and of the remainder 10.1 (range 1.9–24.5). Three cases died during 2000 and a further nine have died since then. During the course of 2000 parents/carers reported seizure episodes in 100/138 (72.5%) cases. Compared with the < 7 years group, cases aged between 7 and 12 years had a higher rate of monthly seizures (Table 2). When comparing classical (n=112) with atypical (n=26) the seizure RR was 0.33 (0.13–0.79) indicating that the seizure rate was significantly lower ($p=0.013$) in the classical cases. When mutation groups were compared, there was no difference in seizure rates overall between those with a *MECP2* mutation and those in whom a mutation was not identified. However those cases with p.R294X and p.R255X mutations and those with mutations in the C-terminal region had significantly lower seizure rates than those without an identified *MECP2* mutation (Table 3). The seizure rate was lower but not significantly so in those with skewed X inactivation.

Cases with abnormal early development and those whose mobility was impaired had increased rates of seizures (Table 4). Those whose parents reported abnormal development both in the period up to six months and in the period from seven to ten months had over twice the rate of seizures of those who had normal development up to ten months ($p=0.07$). Infants who were not moving around or only rolling at ten months had significantly more seizures than those who were walking or crawling at 10 months. Those who had never walked had seizure rates nearly four times that of those who walked normally ($p=0.005$).

In those with seizures, BMI z scores were available on 92/138 (66.7%) and head circumference z scores on 91/138 (65.9%). BMI z scores were generally low, being more than 3 SD below normal for over a quarter of cases. Compared with those whose BMI z scores were in the inter quartile (P_{25} to P_{75}) range, cases with scores in the lower quarter ($<P_{25}$) had an increased rate of seizures ($p=0.03$). One quarter of the 91 cases had head circumference z scores more than 2 SD below the norm for their ages. Compared with those whose head circumference z scores were in the inter quartile range those whose scores were in the lowest quarter of the group were least likely to have seizures ($p=0.01$) but this effect did not remain after age adjustment.

Clinical severity as measured by the Kerr, Percy and Pineda scores correlated positively with seizure rates as did poorer functional ability as measured by the WeeFIM. Although seizure rates were increased in the presence of parent-reported breathing abnormalities and sleep problems the relationship was not statistically significant. One hundred and thirty five subjects had medical appointments, 66 neurological appointments and 51 hospitalizations during 2000. The number of medical appointments ranged from 0 to 40 (median 8) and the number of neurological from 0 to 15 (median 0) per subject (i.e. more than half of the subjects had no neurological appointments). The number of days spent in hospital ranged from 0 to 94 with a median of 0 (i.e. more than half of the subjects had no days in hospital). Rates of seizures were higher in those who had more medical ($p=0.001$) and neurological appointments ($p=0.001$) but not in those with more hospitalizations ($p=0.415$).

During 2000 AEDs were being prescribed to 119/138 (86.2%) of those cases with a diagnosis of epilepsy including 23 in whom no seizures occurred during that year. The most commonly used medications were sodium valproate used by 68 (57%) followed by lamotrigine, used by 52 (44%) and carbamazepine used by 49 (41%) (Table 5). Diazepam presumably as a “rescue” medication was used in 13 cases. The 109 cases on medication in the first month of the study were on 39 different single or combinations of medications with the commonest six being shown in Table 6. For 33 of the groupings there were 3 or less

cases on each. The commonest combinations were sodium valproate and lamotrigine (in 17 cases) followed by carbamazepine and sodium valproate (in 6 cases) and then carbamazepine and lamotrigine (in 5 cases). In the first month of the study 46 (42%) cases were on monotherapy, 42 (39%) on two medications and 21 (19%) on three or more. Those who were on monotherapy with carbamazepine or sodium valproate or a combination of the two had a median of one or less seizures per month. In our group those on lamotrigine or combination therapy with lamotrigine appeared to have higher seizure rates. Overall for the whole year the pattern of medication use varied by age group with younger children less likely to be using those medications classified as “new” such as lamotrigine, topiramate, clobazam, vigabatrin, gabapentin and tigabine (Fig 1). Those who had been prescribed “new” medications also had much higher seizure rates ($p < 0.001$) as did those whose medication had been changed during the year ($p = 0.002$) (Table 7).

4. Discussion

Although seizures are an important comorbidity in Rett syndrome this is the first study to our knowledge to have defined parent-reported seizure rates in a totally ascertained population of cases of Rett syndrome. This analysis combined information reported back by families in a calendar format to the study centre with data on other parameters ascertained from a comprehensive questionnaire completed in the same year. This combined approach yielded detailed information on seizure burden and associated factors in Rett syndrome, as well as AED usage, over a whole year. We were also able to collect information about medical appointments and hospitalizations using a calendar format as previously described,³ which in this analysis helped to further develop the morbidity picture of the group. Families also provided full details of the medications being used by the subjects on a monthly basis. This allowed us to track changes being made to the medication regimen. Although some families did not complete the calendar for every month we were able to adjust for the missing time periods when calculating seizure frequency. In this study we made the decision to accept and focus on those events families felt were seizures⁶ because, irrespective of their aetiology, these are the events that result in a burden for them and their child. We acknowledge this may have resulted in under or over reporting of true epileptic events.¹⁷

Seizures, their unpredictability, frequency and severity, have a considerable impact on the quality of life for all people with epilepsy, but especially in conditions such as Rett syndrome where there are also many other co-morbidities. In a previous study we determined the factors influencing the age of onset of seizures in Rett syndrome.⁶ In this report we have focused on the factors influencing the frequency of seizures. Seizures usually start in Rett syndrome around four years of age with 78.5% having seizures by 10 years.⁶ This is later than in many other conditions with neurological disability. We found seizure rates were highest in the 7–12 age group and appeared to fall after that. This is consistent with previously reported data² and implies that seizures in Rett syndrome “wind down” in late adolescence and adulthood. Almost a quarter of Rett syndrome subjects are not expected to live beyond 25 years,⁴ with nine (6%) of cases in this 2000 calendar cohort deceased by 2006. Our study is only a cross-sectional analysis relating to one calendar year, which means that it is not possible to rule out the possibility of selection bias, particularly arising from deaths.

We found that seizure rates were reduced in subjects with p.R294X, p.R255X and C terminal deletions. Those with the most distal of these mutations (p.R294X and C terminal deletions) also had a significantly reduced seizure onset in the first four years of life.⁶ Other genotype-phenotype relationships observed with these sorts of mutations also indicated milder clinical presentations for other parameters.^{18–21}

Not surprisingly children with early developmental problems as well as those with greater motor disability had a higher frequency of seizures that was additional to the earlier age of onset that we have already reported.⁶ It is known from studies of autonomic function in Rett syndrome²² that breathing abnormalities occur almost universally, although they may not always be noticed by parents or clinicians. What we reported were parent-observed breathing problems which are probably an indication of the more severe hyperventilation or apnoea. We did not find any statistically significant relationship between this parameter or sleep disturbance (again a fairly gross measure) and seizure frequency. Although the BMI in Rett syndrome is generally low, those in the group with a higher BMI appeared to do better, perhaps suggesting that it is important to maximize nutrition. The inverse relationship observed between head growth and seizure rate is surprising, because it appears to conflict with the observations associated with BMI, however, the observation may have been confounded by age and possibly affected by the small sample size. The clinical severity scores described elsewhere² provide a composite picture of clinical severity in Rett syndrome, with some placing more emphasis on the developmental and regression period and less on the current status. They do however include reference to epilepsy. Nevertheless there was a significant correlation with these and seizure frequency suggesting that seizures tend to be worst in those subjects who are already generally severe for other parameters.

The pattern of anticonvulsant use that we recorded in 2000 is similar to the pattern in the report of Steffenburg et al.²³ with some specific differences. In our study sodium valproate was the most commonly used AED, while it was the third most frequently prescribed in the Swedish study, which reported a higher level of lamotrigine/sodium valproate combination usage than we observed. In our study seizure rates were lowest in those on monotherapy with carbamazepine or sodium valproate or on a combination of carbamazepine and sodium valproate. This might suggest that carbamazepine and sodium valproate could have a particular place in the treatment of seizures in Rett syndrome. Caution with this interpretation is warranted because reduction in seizures may not be a response to the medications but it may be that these medications are being used more frequently in those with fewer seizures (such as those in the youngest age group). Not surprisingly, perhaps, children with more difficult epilepsies were more likely to be on the “new” AEDs or on polytherapy.

In total, 42% of cases, who were on AEDs, were on monotherapy, 39% were on 2 AED and 19 % on three or more AED in the first month of the study. A second AED would have been included if seizures were not well controlled on one, so it is not surprising those on two or more AEDs had more seizures than those on one. Current practice in Australia is to try the first line drugs before adding a “new” agent and hence younger children were more likely to be on the older drugs. Only 6/119 were on phenobarbitone or phenytoin which may reflect reluctance in current practice on the part of paediatric neurologists/paediatricians to use these drugs on a long term basis in intellectually disabled children because of the potential cognitive and cosmetic effects. Other than some small studies suggesting benefit with lamotrigine²⁴ and topiramate²⁵ there are no good data on the comparative efficacy of the different AEDs in Rett syndrome.

In summary, we have observed that seizure frequency in children and women with Rett syndrome and epilepsy is age-dependent. The maximal seizure frequency occurs between 7 – 12 years of age with some reduction after this and this is information which will be useful to families and carers. Seizure frequency appears to be higher in those with early onset and more severe developmental disabilities, which may reflect a high general level of cerebral dysfunction in these cases.

On the basis of reports from parents and carers, seizures in Rett syndrome appear to be well controlled in approximately a third of cases (38%), with a further 11% with an earlier diagnosis of epilepsy not using AEDs and having no seizures during the 12 month period of the survey. The spectrum of AEDs used in Australia in 2000 was similar to that reported from other studies.²⁶ Whether the introduction of new AEDs such as levetiracetam and pregabalin and the increased use of established options for epilepsy such as the vagal nerve stimulator²⁷ and the ketogenic diet²⁸ will have a significant role in the management of seizures in Rett syndrome is yet to be determined. A future study using longitudinal data and including clinical information on seizure classification, EEG findings and treatment approaches would aid further definition of the age-related profile we have identified and also assist the task of clarifying the efficacy of the different AEDs.

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Abbreviations

AED	anti-epileptic drug
ARSD	the Australian Rett Syndrome Database
CS2000	calendar study in 2000
FUS2000	follow-up study in 2000
NLS	the nuclear localization signal region
TRD	the transcription repression domain
SD	standard deviation
HC	head circumference
BMI	body mass index
NHMRC	Medical and Health Research Council
APSU	the Australian Paediatric Surveillance Unit

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Fig 1.
Rett syndrome cases on new and old medications by age group

Proportion of Rett syndrome cases with epilepsy and monthly seizure rates in those with a diagnosis of epilepsy by age group

Table 1

Age groups (years) ^a	Number of Rett syndrome cases (%)	Number of cases with an epilepsy diagnosis (%)	Monthly seizure rates			
			<i>b</i> P ₁₀	P ₅₀	P ₉₀	mean (95%CI)
<7	24 (14.8)	16 (66.7)	0	0.2	18.3	3.0 (2.8–3.3)
7–12	45 (27.8)	36 (80.0)	0	2.6	30.3	16.8 (16.4–17.2)
12–17	44 (27.2)	41 (93.2)	0	4.8	16.5	9.1 (8.8–9.4)
>17	49 (30.3)	45 (91.8)	0	0.5	9.8	3.5 (3.4–3.7)
Total	162 (100)	138 (85.2)	0	2.1	18.3	8.7 (8.5–8.8)

^a Age in 2000.

^b 10th 50th and 90th percentile

Table 2

Association of age with seizure rate in Rett syndrome cases with epilepsy

Age groups (years)	n	Seizure rate ratio	95% CI	p
< 7	16	1.00		
7–12	36	4.47	1.32–15.16	0.016
12–17	41	2.42	0.73–8.00	0.149
>17	45	1.17	0.36–3.81	0.791

Table 3

Association of mutation with seizure rate in Rett syndrome cases with epilepsy

MECP2 mutations	n	Seizure rate ratio	95% CI	p
No mutation	29	1.00		
Mutation identified	102	0.64	0.27–1.51	0.302
No mutation	29	1.00		
p.T158M	11	2.50	0.65–9.67	0.184
p.R168X	13	0.37	0.10–1.32	0.125
p.R294X	7	0.12	0.02–0.60	0.010
p.R270X	12	0.51	0.14–1.91	0.320
p.R255X	6	0.11	0.02–0.68	0.017
p.R133C	7	0.80	0.16–4.03	0.792
p.R306C	6	0.35	0.06–1.96	0.234
p.R106W	3	0.17	0.02–1.77	0.139
C terminal	13	0.15	0.04–0.54	0.004
Early truncating ^a	8	0.62	0.14–2.87	0.545
Large deletions	5	0.72	0.11–4.58	0.727
Others	11	0.53	0.14–2.05	0.358
Random XCI	54	1.00		
Skewed XCI	43	0.55	0.23–1.33	0.185

^aNot including p.R270X, p.R255X and p.R168X

Table 4

Association of developmental factors and markers of clinical severity with seizure rate in Rett syndrome cases with epilepsy

	No	Seizure rate ratio	95% CI	p
Ambulation				
Walked <18mths	33	1.00		
Walked <18mths then lost/walked ≥18mths	22	2.12	0.69–6.52	0.188
Walked 18–30mths then lost/walked >30mths	20	2.19	0.69–6.95	0.183
Never walked	52	3.69	1.49–9.15	0.005
Mobility at 10 months				
Walking/ crawling	32	1.00		
Bottom-shuffling	32	1.46	0.53–4.00	0.462
Rolling	43	3.35	1.31–8.57	0.012
Not moving around	27	5.60	1.95–16.02	0.001
Abnormal development within 0–10 months				
No problems	35	1.00		
0–6 months only	44	1.67	0.65–4.24	0.284
0–6 and 7–10 months	58	2.25	0.93–5.44	0.072
Respiratory dysfunction				
No	22	1.00		
Yes	101	1.85	0.69–4.94	0.219
Sleep disturbance				
No	15	1.00		
Sleep disturbance past only	27	1.30	0.35–4.90	0.698
Sleep disturbance past and present	84	1.99	0.63–6.30	0.244
Body mass index z- score in 2000				
P ₂₅ to P ₇₅ (−3.23~ 0.36)	47	1.00		
< P ₂₅ (−9.08~−3.23)	25	3.07	1.14–8.30	0.027
> P ₇₅ (0.36~ 2.82)	20	0.95	0.33–2.78	0.928
Head circumference z-score in 2000				
P ₂₅ to P ₇₅ (−2.18~ −0.53)	45	1.00		
< P ₂₅ (−4.88~−2.18)	25	0.29	0.11–0.77	0.014
> P ₇₅ (−0.53~ 2.18)	21	0.52	0.18–1.48	0.219
WeeFIM score	127	0.96	0.93–0.99	0.007
Kerr score	127	1.08	0.99–1.17	0.081
Percy score	127	1.08	1.01–1.16	0.021
Pineda score	127	1.11	1.03–1.21	0.010
Hospital admission	138	1.03	0.95–1.12	0.415

	No	Seizure rate ratio	95% CI	p
Total medical appointment	138	1.07	1.03–1.11	0.001
Neurological appointment	138	1.33	1.12–1.58	0.001

Table 5

Range of anti-epileptic medications ever used during 2000 by age group

Medication(s)	Rett syndrome cases ever on this medication/combination ^a				
	0-7y (n=12)	7-12y (n=32)	12-17y (n=36)	>17y (n=39)	Total (n=119)
Sodium valproate	6	17	22	23	68
Lamotrigine ^b	1	16	21	14	52
Carbamazepine	3	13	13	20	49
Topiramate ^b	0	3	8	5	16
Clonazepam	1	4	4	5	14
Diazepam	1	5	1	6	13
Clobazam ^b	0	4	6	2	12
Vigabatrin ^b	0	3	3	1	7
Nitrazepam	1	3	1	0	5
Gabapentin ^b	1	1	1	1	4
Phenytoin sodium	1	0	1	2	4
Phenobarbital	0	1	1	0	2
Tiagabine ^b	0	1	0	1	2
Primidone	0	0	0	1	1

^aIncluding used in combination

^bNew medication

Commonest AEDs (and combinations) used in January of 2000 and associated seizure rates and median age of subjects

Table 6

Medication(s)	Cases on this medication/combination	Median age	Monthly seizure rate			
			P ₁₀	P ₅₀	P ₉₀	mean (95%CI)
Carbamazepine	19	15.5	0.0	0.6	15.3	3.4 (3.1–3.6)
Sodium valproate +lamotrigine	17	13.8	0.1	3.8	30.3	26.2 (25.5–29.6)
Sodium valproate	16	10.5	0.0	0.2	13.7	3.4 (3.1–3.7)
Carbamazepine +sodium valproate	6	16.5	0.0	1.0	2.8	1.2 (0.9–2.0)
Lamotrigine	5	9.7	0.0	2.8	24.8	7.6 (6.9–8.3)
Carbamazepine +lamotrigine	5	14.1	0.5	5.4	30.3	9.0 (8.2–9.3)

Table 7

Relationship between seizure rates and the use of “new” medications and requirement for medication change during 2000

n	Monthly seizure rate		Seizure rate ratio	95% CI	p
	P ₁₀	P ₅₀	P ₉₀		
On new medication(s)					
No	55	0.0	0.5	10.0	1.00
Yes	64	0.1	4.9	30.1	3.74
					1.93–7.22
Change medication(s) ^a					
No	92	0.0	2.1	15.3	1.00
Yes	27	0.2	4.9	35.1	3.41
					1.55–7.52

^aExclude cases using the same medication or medication combinations but off and on in various months