# Effect of lamotrigine on cognition in children with epilepsy

R.M. Pressler MD; C.D. Binnie MD; S.G. Coleshill PhD; G.A. Chorley; and R.O. Robinson FRCPCH

From the Department of Clinical Neurophysiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK (Drs. Pressler, Coleshill, Chorley and Professor Binnie); and Department of Pediatric Neurology, Guy's Hospital, St Thomas Street, London SE1 9RT, UK (Professor Robinson)

**Address for correspondence**

Dr. Ronit M. Pressler

Department of Clinical Neurophysiology

National Hospital for Neurology and Neurosurgery

Queen Square

London WC1N 3BG

UK

Tel (44) 20 7837 3611

Fax (44) 20 7829 8720

ronit.pressler@uclh.org

# Article abstract

*Background*: Lamotrigine does not affect cognition in healthy adult volunteers or adult patients with epilepsy, but its effect on cognition in children is uncertain.

*Objective*: To compare the effect of lamotrigine and placebo on cognition in children with well-controlled or mild epilepsy.

*Method*: In a double blind, placebo-controlled, cross-over study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine. Each treatment phase was 9 weeks, the cross-over period 5 weeks. A neuropsychological test battery was performed during EEG monitoring at baseline and at the end of placebo and drug phases. The paired Student's t-test was used for statistical analysis for neuropsychological data (2-tailed) with a p-value of 0.01 considered significant. Carry-over and period effect were analyzed with generalized linear modeling (SPSS 10).

*Results*: Forty-eight children completed the study. Seizure frequency was similar during both treatment phases. No significant difference was found in continuous performance, binary choice reaction time, verbal and non-verbal recognition, computerized visual searching task, verbal and spatial delayed recognition and verbal and non-verbal working memory between placebo and lamotrigine treatment phase. There was no significant carry-over and period effect when corrected for randomization.

*Conclusion*: Lamotrigine exhibits no clinically significant cognitive effects in adjunctive therapy for children with epilepsy.

Over 100 studies have investigated the cognitive side effects of antiepileptic drugs (AEDs), mostly in adults. Many of these studies were criticized for small sample size, short observation period, open label studies, no or inappropriate controls, no or inadequate randomization and inappropriate statistical methods.[1] A further confounding factor can be an improvement of seizure control during active treatment. Seizure frequency is known to influence cognitive performance, thus better seizure control may conceal a potential negative effect of an AED.

Even modest cognitive side effects in children may have significant consequences because they can influence learning of new skills and the ability to develop social strategies.[2] Cognitive impairment is likely to occur with phenobarbitone, may occur with phenytoin and carbamazepine and is less evident with sodium valproate.[3] Despite the rising concern about the effect of AEDs on neurodevelopment there are very few controlled studies examining the cognitive effects of newer AEDs in this population.

Studies in adults suggest that lamotrigine is better tolerated than most long-established antiepileptic drugs. Sedation and other CNS side effects in particular are less common and quality-of-life studies suggest that it has comparatively few cognitive side effects.[4] Only limited data exists on formal cognitive test performance in adults. Meador et al. directly compared the cognitive and behavioral effects of carbamazepine and lamotrigine in 25 healthy adults using a double-blind, randomized, crossover design with two 10-week treatment periods. Test results on lamotrigine were significantly better compared to results on carbamazepine in more than half of the 40 variables (e.g., cognitive speed, memory, mood factors, sedation, perception of cognitive performance, and other quality of life perceptions).[5] Similar results were reported by others.[6,7] In adult patients with refractory epilepsy lamotrigine did not differ from placebo in its effect on concentration and psychomotor performance.[8,9]

There are few open studies and case reports in children suggesting that lamotrigine has a similar CNS profile in children[10,11] but there is no randomized and controlled study using formal

neuropsychological testing. We conducted the first placebo controlled study on the cognitive effects of lamotrigine in children with epilepsy.

## Methods

*Patients*

Patients were recruited between September 1996 and January 1998 from pediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE, formerly St Piers Lingfield), UK. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/carers felt that further adjustments to AEDs were not warranted. The inclusion criteria for 'occasional seizures' took account of seizure severity and were defined as: no more than one generalized tonic-clonic seizure in the last six months, no more than one complex partial seizure or two simple partial seizures in the last month, no more than five absences occurring on any one day within the last three months. Other inclusion criteria were an IQ of $\geq 70$ or mental age of at least 7 years. For ethical reasons, some evidence of cognitive impairment or psychosocial dysfunction was required to justify participation. Specifically, parents were sufficiently concerned about their child's behavior or cognition to seek help. The protocol was approved by the ethics committees at all three study sites and written informed consent was obtained from all parents and all patients aged 16 years or over. Oral agreement was obtained from patients aged less than 16 years.

*Methods*

Patients were randomly assigned to receive lamotrigine (Lamictal, GlaxoWellcome, now GlaxoSmithKline, Stevenage, UK) followed by placebo or placebo followed by lamotrigine in addition to the current antiepileptic drug regime. During an initial 4-week single blind phase all

subjects received placebo to familiarize patients and parents with trial procedures and to provide a reference point if the subsequent phases showed an order effect. The initial drug escalation was over 4 weeks and the first treatment phase 9 weeks followed by a 5 week cross-over phase and the second treatment phase of 9 weeks (figure E-1 on the *Neurology* web site: www.neurology.org). Randomization was computer generated in blocks of four with randomization stratified by the presence or absence of interictal EEG discharges. Details of study protocol and randomization have been published elsewhere.[12] The dose of lamotrigine depended on age, weight and concomitant AEDs according to the recommendations current at the time the study was conducted. For children on sodium valproate lamotrigine was escalated to 2 mg/kg/day (12≤years old) or 150 mg/day (>12 years old). For children not on sodium valproate lamotrigine was escalated to 10 mg/kg/day (12≤years old) or 300 mg/day (>12 years old). All investigators and patients/parents were blinded to group assignment until after all patients had completed the study. At entry, physical and neurological examination, history, routine and ambulatory EEG, standard biochemical tests, antiepileptic drug concentrations, neuropsychological tests and IQ tests (Wechsler Intelligence Scale for Children, WISC-III) were performed and behavioral scales completed by parents and teachers. Patients were assessed at the end of each treatment phase after eight weeks on a stable dose (weeks 17 and 31) when the following were performed: physical examination, lamotrigine blood levels, ambulatory EEG, neuropsychological tests, behavioral scales for parents and teachers and documentation of compliance, seizures and possible adverse events. Seizures were classified according to the criteria of the International League against Epilepsy.

Ambulatory monitoring was performed for a 12 to 24 hour period using the Oxford Medilog 8-channel cassette system or the digital Embla recording system. EEG recordings were analyzed visually and epileptiform discharges were defined as spikes, sharp waves, spike wave complexes or multiple spike discharges. Discharges were considered subclinical where 'the available

methods of clinical observation, applied under particular circumstances, failed to show any changes in the patient'.[13]

Behavior was assessed with the Conners' Rating Scales for parents and teachers. For more detail on methods of ambulatory EEG analysis and behavioral assessment see Pressler et al.[12] The following computerized cognitive tests were performed at baseline and the end of both placebo and lamotrigine treatment phases during EEG monitoring. All tests were considered suitable for repeat testing.

- *FePsy Recognition Probe Test:* We used the verbal and non-verbal subtests with 2, 4 or 6 words and 3 or 4 figures according to clinically assessed memory span abilities (remaining constant throughout the study).[14] Both number of correct responses and reaction time were recorded.

- *Yes-No Delayed Recognition Test (serial matching to sample tests: SMTS-16):* 'Words' and 'Faces' have been shown to be sensitive to hemispherically lateralized cognitive deficits in patients with temporal lobe epilepsy.[15] The main outcome measure of the test is the number of items (words or faces) correctly identified as targets minus the number of items incorrectly identified ($d'$ = discrimination score). The test also measures "yes" or "no" response bias ($c'$ = bias score). Two outcome measures derived from Signal Detection Theory[16] were computed on the test data, where *d' (discrimination)*= z(Hits) – z(False Alarms), and *c' (*'yes' or 'no' *Response Bias)* = -0.5 [z(Hits) + z(False Alarms].

- *FePsy Computerized Visual Searching Task (CVST)* with 10 patterns for younger and 24 patterns for older children. Error rate and reaction time give an indication of the accuracy of information processing and mental speed which have been proven useful in evaluating cognitive effects of anticonvulsants.[14]

- *Binary Choice Reaction Time Test:* In a computerized binary choice reaction time task the target (a tiger) is shown on the left or right hand side of the computer screen and the patient has to press the key of the keyboard with the corresponding left or right hand. The speed of

presentation was self-paced. Thirty stimuli were presented each side, with positions pseudo-randomized. The median reaction speed and accuracy for each hand were recorded. By introducing a decision component the reaction time reflects not only motor speed but also the decision making process.

- *Continuous Performance Test (Tracker test):* This is a computerized test of sustained attention and vigilance. A target moving randomly around the touch-screen has to be followed with the index finger. The variable of interest was the difficulty level achieved, based on achieving more than 40% of the time on target. It was performed without EEG co-registration.

- *Ngrams Working Memory Test:* The Ngrams test[17] measures working memory and has been developed from the computerized 'Modified Corsi' test.[13] Words for Ngrams-Words were matched for frequency, age-of-acquisition, imagery and concreteness. The test consists of presenting a sequential string of items on a touch-screen within a 3x4 spatial array in a pseudo-randomized sequence. Recall of the string was indicated by the subject by touch-selecting items from a menu of 12 possibles, then entering them into the array. String length was automatically adapted to each patient's working memory capacity ranging from three to five items. Outcome measures are reaction time and a derived compound score as a general measure of performance. Thus for Ngrams-Words the compound score includes indices for item identity and sequential order of identity and item location and sequential order of location, while for Ngrams-Corsi the compound score combines only the latter two indices.

*Analysis*

The primary analysis was a series of paired t-tests for placebo versus lamotrigine across the neuropsychological variables. As 13 variables were examined the level of significance was reduced to 0.01 to correct for multiple comparisons. If the correct Bonferroni method (c= k!/2!(k-2)!) were to be used, only a p-value of 0.001 would be considered significant. As we were concerned to detect a possible deterioration of cognition, a significance level of 0.01 errs on the

side of caution. To inspect the consistency of the findings and because extreme values were anticipated, data were also analyzed by comparing the raw means for all variables using the non-parametric Sign test. If significant differences between placebo and active treatment were detected an ANCOVA would be used to exclude effects due to multiple comparisons. An ANCOVA with Greenhouse-Geisser test was used to examine period and carry-over effects as well as to examine whether the effect of lamotrigine on discharges influenced the result (with 'reduction of discharges' comprising a between-subjects factor). Analysis was by intension to treat.

## *Results*

Of the 64 children screened, 61 were included (39 boys, mean age: 11.5 years, range 7-17 years). Sixteen children had idiopathic partial epilepsy, 19 had idiopathic generalized epilepsy and 26 had symptomatic partial epilepsy. Forty-one children had interictal discharges in the initial ambulatory recording. All patients underwent randomization and entered the single-blind baseline phase; 31 were randomized to receive first lamotrigine and then placebo and 30 in the reverse order (figure E-1 on the *Neurology* web site: www.neurology.org). However, two children were not enrolled in the treatment phase: seizure control deteriorated in one child and the parents of the other withdrew consent. The demographic characteristics of both groups were similar (table E-1 on the *Neurology* web side: www.neurology.org). Lamotrigine levels according to dose and concomitant AED were as follows: ≤ 12y (2 mg/kg), on sodium valproate: mean 7.6µg/ml (SD ±4.3); ≤ 12y (10 mg/kg), not on sodium valproate: mean 3.5µg/ml (SD ±2.4); >12y (150 mg), on sodium valproate: mean 8.9µg/ml (SD ±1.2); >12y (300 mg), not on sodium valproate: mean 4.6µg/ml (SD ±3.5).

*Effect of lamotrigine on frequency of seizures and interictal EEG-discharges*

Seizure frequency did not change significantly during the study. In the three months preceding baseline the mean seizure frequency was 3.43 (SD 13.4, range 0-90) seizures per month, during

the placebo phase 3.24 (SD 10.38, range 0-50) seizures per month and during the lamotrigine phase 3.21 (SD 14.69, range 0-90). Twenty-one patients (44%) had a reduced frequency of discharges, whilst 16 patients (33%) either had no change or an increase in the frequency of discharges and 11 patients (23%) had no discharges during either lamotrigine or placebo phase. Twenty-three patients (48%) had a reduced duration of discharges whilst 14 patients (29%) either had no change or an increase of discharge duration and 11 patients (23%) had no discharges in either lamotrigine or placebo phase. Cessation of all interictal discharges during lamotrigine phase was seen in five patients. The effect of lamotrigine on discharges was similar across the types of epilepsies. For more detailed results see Pressler et al.[12]

*Adverse events*

Adverse events were evaluated for 59 patients after exclusion of the two patients who were withdrawn in the single blind baseline phase. Apparent treatment related adverse events were observed in 23 of 59 patients (39%) during the lamotrigine phase and in 19 of 52 patients (37%) in the placebo phase (Table 1). Of the seven children who developed a rash during the lamotrigine phase, three were on sodium valproate, two on carbamazepine and two on no other antiepileptic drugs. All adverse events were mild and transient. Adverse events led to withdrawal from the study of six patients (all during lamotrigine phase): in five due to a rash and in one due to dizziness and nausea. The latter was later found to have a high phenytoin level of 32µg/ml.

*Effect of lamotrigine on neuropsychological performance*

The means of neuropsychological test results for baseline, placebo and lamotrigine (±SD) are given in Table 2. Comparison of mean values of performance on placebo with those on lamotrigine revealed slightly better performance on lamotrigine in one variable (CVST error rate), no change in seven (FePsy recognition non-verbal score, binary choice reaction time right and left hand, continuous performance test, Ngrams-Corsi compound score, Ngrams-Corsi reaction time,

Ngrams-Words compound score) and slight deterioration of performance in five (FePsy recognition verbal score, delayed recognition faces and words, CVST reaction time, Ngrams-Words reaction time). None of these differences were significant for p=0.01 (Table 2).

The Sign tests similarly showed that the number of means favoring one condition over the other was not significant in any of the 13 variables (Table 2). Thus, no condition was superior over the other for any of the variables.

There was no significant difference between patients with a reduction of discharges during active treatment and patients without a reduction in discharge frequency in respect to the effect of lamotrigine on cognition (number of discharges: $F(26,86)=1.95$; ns; duration of discharges: $F(26,86)=1.81$; ns).

An ANCOVA with repeated measures was used to examine period and carry-over effects. Test values of first, second and third test session were compared with randomization as the between-subject factor. In 10 out of 13 variables each consecutive session produced a better result. For two variables (FePsy non-verbal recognition and continuous performance test) the second session was better than the third and in one (delayed recognition faces) the first session was better than the second and the third was best. Comparison using ANCOVA with repeated measures reveals a tendency for each consecutive test to show better performance, but this did not reach significance at a 0.01 level ($F(26,98)=1.64$; p=0.02). Four out of the 13 variables showed significance at a 0.05 level: binary choice reaction (right and left hand), CVST error rate and reaction time. All significant variables showed the typical learning profile, with each consecutive session improving. However, when randomization was taken into account, there was no significant difference between sessions ($F(26,98)=1.07$; p=0.4).

In the delayed recognition test (SMTS-16) there was no relevant response bias at baseline, or on placebo or lamotrigine in either of the tests (faces/words). Thus response bias scores fell within a small range around neutral bias (mean ±SD for 'faces' at baseline: 0.8±0.25; at placebo:

0.14±0.25; at lamotrigine: 0.3±0.29; for 'words' at baseline: 0.12±0.28, at placebo: 0.16±0.24; at lamotrigine 0.2±0.25). No significant change in bias comparing placebo with lamotrigine was found.

Cognitive side effects of lamotrigine were similar in patients with and without reduction of discharges during lamotrigine treatment. Table E-2 on the *Neurology* web site (www.neurology.org) shows the mean differences of test results placebo and lamotrigine between the two patient groups. Using ANCOVA there was no significant difference between them (the number of discharges: $F(26,86)=1.95$; ns; duration of discharges: $F(26,86)=1.81$;ns). The number of patients with complete suppression of discharges was too small for statistical analysis.

## *Discussion*

In this controlled study evaluating cognitive side effects of lamotrigine in children with mild epilepsy using formal cognitive testing we report no significant cognitive impairment during active treatment compared with placebo. Our findings are concordant with previous reports in healthy volunteers[5,6,7] and adults with epilepsy.[9,18] Due to our double blind, placebo-controlled, cross-over design, patient selection and broad test battery employed for this study, we have avoided several methodological pitfalls described earlier.[1,3]

We found a tendency for test performance to improve with each consecutive session. This improvement can be plausibly explained by a learning effect but a placebo effect has to be considered also. Despite the use of tests thought to be appropriate for serial testing such as choice reaction time or the CVST we nevertheless found a learning effect. This illustrates the importance of using appropriate randomization methods and a control group, as in our study. It also demonstrates the fallibility of studies where the cognitive function of the active drug phase is compared to baseline.[9]

Animal experiments suggest that lamotrigine has no effect on either the induction or the maintenance of long-term potentiation of memory fuction[19] and may even protect against excitotoxic and ischemic insults.[20]

Several uncontrolled studies have reported improved psychosocial functioning during lamotrigine treatment in patients with epilepsy. This included concentration, school or work performance and behavior, particularly in children with learning difficulties.[10,21] The following confounding factors have to be considered in the open studies without formal testing: (1) bias in patient selection (2) placebo effect, (3) reduction of seizure frequency during active treatment, (4) spontaneous fluctuations of seizure variables and EEG abnormalities (5) spontaneous fluctuations of cognition and behavior in patients with learning difficulties.

A higher seizure frequency is associated with an impairment of cognition and behavior.[22, 23] Thus, a reduction of seizure frequency may result in improvement of cognitive function and behavior. Even a small change of seizure frequency may have an impact, or changes in seizure severity may have cognitive effects in some patients even if the absolute number of seizures remains the same. Furthermore, it is unclear whether EEG discharges improved in these patients. In our study we avoided this confounding factor by studying patients with mild or well-controlled epilepsy. Yet a drastic improvement in behavior and cognition has been described in patients with a reduction of discharges even when no change in seizure frequency was observed.[24] The subjective improvement of cognition in quality of life measurements described in open and controlled studies[4,8] may also be explained by improvement in mood.[25]

Most controlled studies in either healthy volunteers or adult patients with epilepsy could not confirm an improvement in cognitive performance using formal and controlled testing. Only Aldenkamp and colleagues[7] found evidence for a positive effect of lamotrigine on cognition. There are however, several methodological shortcomings[26] including (1) incomparable doses of antiepileptic drugs, (2) inconsistent changes of test results, for example in a visual reaction time test, results using the dominant hand were better for placebo, but the results using the non-

dominant hand were better for lamotrigine, (3) inappropriate statistical methods, (4) possible

confounding factors (5) the use of a parallel design with small numbers of volunteers. Thus, the

findings may have been due to chance and may lack clinical relevance.[26]

We could not detect a significant improvement of cognitive function in any of our variables. Most

of our patients were seizure-free and in the remaining patients seizure frequency did not change

significantly. Thus, seizure frequency was not a confounding factor in contrast to many open

studies described above. There is evidence that interictal discharges are associated with cognitive

impairment[13] and a reduction of discharges may be associated with an improvement in

cognition.[21,24] However, we found no difference in the cognitive effects of lamotrigine in patients

with or without reduction of discharges. This may be explained by the fact that there was only a

relatively small effect on discharges in our group of patients with mild or well-controlled

epilepsy.[12] This is in contrast to patients with severe or on-going epilepsy where lamotrigine

significantly reduced interictal discharges.[21,24] The effect of lamotrigine on cognition may be

clinically only relevant in patients with more severe epilepsy and greater suppression of

discharges. Nevertheless we described a significant improvement of behavior in those patients

with a reduction of discharges compared to patients without change in discharges.[12] Cognitive

function may be more susceptible to the amount and duration of discharges occurring during the

test[13,27], rather than changes within a 24-hour period. Thus, a measurable effect may only be

expected if there is a cessation of all discharges.

In contrast, aggressive behavior has been associated with lamotrigine, particularly in children and

adults with learning difficulties.[11,28] However, no formal cognitive testing or behavioral scales

were used. It has been suggested that this behavior is related to patients becoming more alert,

active, and demanding. Insomnia has also been reported in a small proportion of patients[29], but

most of these patients were taking a relatively high dose of lamotrigine. In addition, 'being more

alert' and 'suffering from insomnia' are changes, which relate to the same process.

Although a proportion of the children were recruited from tertiary referral centres, our group of patients is representative in respect to the distribution of epilepsy syndromes and response to treatment in school-age children with epilepsy: nearly 50% have symptomatic epilepsies, 25% idiopathic partial epilepsies, 25% idiopathic generalised epilepsies and about 70% of children are well controlled on one or two AEDs. The results of our study suggest that lamotrigine per se has minimal or no cognitive side effects in children with epilepsy. Further studies are needed to evaluate the effects of lamotrigine on cognition in children taking monotherapy, especially with newly diagnosed epilepsy. In addition, longer term studies in children directly comparing AEDs, which have demonstrated differential cognitive effects in adults, are needed to determine if AEDs differentially impact cognitive neurodevelopment.

## Acknowledgements

# References

1. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001;357:216-222.

2. Stafstrom CE. Assessing the behavioral and cognitive effects of seizures on the developing brain. Prog Brain Res 2002;135:377-390.

3. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology 2004;62:872-877.

4. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995;345:476-479.

5. Meador KJ, Loring DW, Ray PG, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology 2001;56:1177-1182.

6. Martin R, Kuzniecky R, Ho S, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology 1999;52:321-327.

7. Aldenkamp AP, Arends J, Bootsma HP, et al. Randomized double-blind parallel-group study comparing cognitive effects of a low-dose lamotrigine with valproate and placebo in healthy volunteers. Epilepsia 2002;43:19-26.

8. Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. Epilepsia 1993;34:312-322.

9. Placidi F, Marciani MG, Diomedi M, et al. Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand 2000;102:81-86.

10. Uvebrant P, Bauziene R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure-related benefits. Neuropediatrics 1994;25:284-289.

11. Besag FM, Wallace SJ, Dulac O, Alving J, Spencer SC, Hosking G. Lamotrigine for the treatment of epilepsy in childhood. J Pediatr 1995; 27:991-997.

12. Pressler RM, Robinson RO, Wilson GA, Binnie CD. Treatment of interictal epileptiform discharges can improve behavior in children with behavioral problems and epilepsy. J Pediatr 2005;146:112-117.

13. Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. Brain 1984;107:293-308.

14. Aldenkamp AP, Alpherts WC, Dekker MJ, Overweg J. Neuropsychological aspects of learning disabilities in epilepsy. Epilepsia 1990;31Suppl 4:S9-20.

15. Coleshill SG, Binnie CD, Morris RG, et al. Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J Neurosci. 2004;24:1612-1616.

16. MacMillan NA, Creelman CD. Detection Theory: A User's Guide. Cambridge: Cambridge UP, 1991.

17. Coleshill SG. PhD thesis: Neuropsychological correlates of unilateral mesial temporal sclerosis and alternate unilateral subthreshold electrical stimulation of the hippocampus. London: London University, 1999.

18. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999;37:81-87.

19. Xiong ZQ, Stringer JL. Effects of felbamate, gabapentin and lamotrigine on seizure parameters and excitability in the rat hippocampus. Epilepsy Res 1997;27:187-194.

20. Smith SE, Meldrum BS. Cerebroprotective effect of lamotrigine after focal ischemia in rats. Stroke 1995;26:117-121.

21. Eriksson AS, Knutsson E, Nergardh A. The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. Epilepsia 2001;42:230-236.

22. Farwell JR, Dodrill CB, Batzel LW. Neuropsychological abilities of children with epilepsy. Epilepsia 1985;26:395-400.

23. Keith HM, Ewert JC, Green MW, Gage RP. Mental status of children with convulsive disorders. Neurology 1955;5:419-425.

24. Besag FM. Lamotrigine in the management of subtle seizures. Rev Contemporary Pharmacother 1995;5:123-131.

25. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64:1013-1024.

26. Dodrill CB.Thoughts on Aldenkamp et al.'s article. Epilepsia. 2002;43:1597.

27. Binnie CD. Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG? Lancet Neurol 2003;2:725-730.

28. Ettinger AB, Weisbrot DM, Saracco J, Dhoon A, Kanner A, Devinsky O. Positive and negative psychotropic effects of lamotrigine in patients with epilepsy and mental retardation. Epilepsia 1998;39:874-877.

29. Sadler M. Lamotrigine associated with insomnia. Epilepsia 1999;40:322-325.

**Table 1**: Most frequently reported drug related adverse events

|  | Number of patients (%) | |
| --- | --- | --- |
| **Adverse Event** | **Lamotrigine (n=59)** | **Placebo (n=52)** |
| Cold or viral illness | 9 (15) | 9 (17) |
| Rash | 7 (12) | 2 (4) |
| Nausea | 5 (8) | 2 (4) |
| Injury or accident | 4 (7) | 0 |
| Pharyngitis | 4 (7) | 1 (2) |
| Headache | 1 (2) | 2 (4) |
| Dizziness | 1 (2) | 2 (4) |
| Abdominal pain | 0 | 2 (4) |
| Patients withdrawn | 6 (10) | 0 |

**Table 2**: Mean scores, reaction times and difference between placebo and lamotrigine as well as results of paired-t tests and Sign test. Mean **δ**: mean difference between placebo and lamotrigine. * higher score signify a worse result. ‡Binomial distribution used.

| | Mean (±SD) | | | Paired t-test | | Sign test | |
|---|---|---|---|---|---|---|---|
| | Baseline | Placebo | Lamotrigine | Mean δ (±SD) | p value | Z | p value |
| FePsy Recognition verbal | 18.2 (3.7) | 19.6 (3.4) | 19.1 (3.5) | 0.7 (2.4) | 0.07 | -1.64 | 0.10 |
| FePsy Recognition non-verbal | 14.5 (3.3) | 15.1 (3.8) | 15.1 (3.5) | 0.3 (3.1) | 0.60 | -0.74 | 0.46 |
| Delayed recognition, faces | 2.1 (0.8) | 2.4 (0.6) | 2.2 (0.7) | 0.2 (0.7) | 0.14 | 0.00 | 1.00 |
| Delayed recognition, words | 2.2 (0.8) | 2.6 (0.7) | 2.4 (0.8) | 0.2 (0.7) | 0.17 | -1.44 | 0.15 |
| CVST, error rate* | 1.4 (2.1) | 0.8 (1.5) | 0.6 (1.2) | -0.3 (1.2) | 0.14 | ‡ | 0.26 |
| CVST, reaction time* | 8.2 (3.5) | 7.0 (1.9) | 7.4 (2.2) | -0.4 (1.6) | 0.14 | 0.00 | 1.00 |
| Binary choice reaction right * | 0.5 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.0 (0.1) | 0.52 | -0.31 | 0.76 |
| Binary choice reaction left * | 0.4 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.0 (0.1) | 0.06 | -1.19 | 0.23 |
| Continuous performance test | 5.8 (1.5) | 6.4 (1.2) | 6.4 (1.1) | 0.0 (1.1) | 1.00 | ‡ | 1.00 |
| Ngrams-Corsi compound | 0.7 (0.2) | 0.8 (0.2) | 0.8 (0.1) | 0.0 (0.1) | 0.34 | -.47 | 0.64 |
| Ngrams-Corsi reaction time * | 1.4 (0.8) | 1.1 (0.3) | 1.1 (0.4) | -0.1 (0.3) | 0.05 | -2.14 | 0.03 |
| Ngrams-Words compound | 0.7 (0.1) | 0.7 (0.1) | 0.7 (0.1) | 0.0 (0.1) | 0.66 | -0.15 | 0.88 |
| Ngrams-Words reaction time * | 3.7 (1.5) | 3.4 (1.5) | 3.6 (1.1) | -0.2 (1.2) | 0.23 | -1.83 | 0.07 |