# TREATMENT OF INTERICTAL EPILEPTIFORM DISCHARGES CAN IMPROVE BEHAVIOR IN CHILDREN WITH BEHAVIORAL PROBLEMS AND EPILEPSY

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**Objectives** It is generally agreed that children should be treated for epilepsy only if they have clinical seizures. The aim of this study was to examine whether suppressing interictal discharges can affect behavior in children with epilepsy.

**Study design** In a double-blinded, placebo-controlled, crossover 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. Ambulatory electroencephalographic recordings and behavioral scales were performed during baseline and at the end of placebo and drug phases. The primary hypothesis to be tested was that behavioral scales would improve specifically in patients with a reduction of electroencephalographic discharges during active drug treatment.

**Results** Global rating of behavior significantly improved only in patients who showed a significant reduction in either frequency ($P < .05$) or duration of discharges ($P < .05$) during active treatment but not in patients with without a significant change in discharge rate. This improvement was mainly seen in patients with partial epilepsy ($P < .005$).

**Conclusions** Our data suggest that suppressing interictal discharges can improve behavior in children with epilepsy and behavioral problems, particularly partial epilepsy. Focal discharges may be involved in the underlying mechanisms of behavioral problems in epilepsy. *(J Pediatr 2005;146:112-7)*

Children with epilepsy are at a higher risk for development of behavioral problems and psychiatric disorders than are their healthy peers[1] or children with other chronic disease.[2] This is not only important for children with uncontrolled epilepsy and learning difficulties but also for the majority of children with epilepsy whose seizures respond well to antiepileptic drugs (AEDs) and who are educated in mainstream schools. Such children have been found to have more learning and behavioral problems in school compared with matched control children and achieve less than expected for their age and IQ.[3,4]

Increased behavioral problems in children with epilepsy are a consequence of a number of interacting influences including underlying brain lesion, age of onset, AEDs, psychosocial issues, seizure type and frequency, and interictal abnormalities in the electroencephalogram.[5,6] Interictal discharges or subclinical epileptiform discharges occur in up to 80% of patients with ongoing epilepsy, although they may not be seen in every EEG recording.[7] The clinical relevance of these discharges is unclear; specifically, it is uncertain whether they are truly subclinical or cause brief disruptions of cognitive function (as described by Aarts et al[8] as transitory cognitive impairment) and behavior.[9] The only way to determine whether discharges cause cognitive and behavioral problems in children with epilepsy is by finding whether cognition and behavior improve when epileptiform discharges are suppressed.

It is generally agreed by neurologists and pediatricians that patients should be treated for epilepsy only if they have clinical seizures. Treating the EEG, so-called "EEG cosmetics," is generally condemned.

We aimed to test this view by performing a double-blinded, placebo-controlled, crossover trial to examine whether suppressing interictal discharges can improve behavior

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| AED | Antiepileptic drug | TCI | Transitory cognitive impairment |
| MANOVA | Multivariate analysis of variance | EEG | Electroencephalography |
| NCYPE | National Centre for Young People with Epilepsy | | |

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in children with epilepsy and by implication whether interictal discharges can cause psychosocial dysfunction. To avoid the confounding factor of changing seizure frequency on behavior, we included only patients who were seizure free or who had infrequent seizures. It was essential to exclude an independent psychotropic effect of the drug on behavior and thus we included both patients with and without interictal discharges. Consequently, it was possible to compare behavioral changes in patients with and without a reduction of interictal discharges.

## METHODS

Patients were recruited 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), United Kingdom. Additional patients were referred to the study sites from hospitals in the South Thames Region. Patients 7 to 17 years of age were eligible if they had a diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent believed that further adjustments to AEDs was not warranted. The inclusion criteria for "occasional seizures" took account of seizure severity and were defined as no more than 1 generalized tonic-clonic seizure in the last 6 months or no more than 1 complex partial seizure or 2 simple partial seizures in the last month or no more than 5 absences occurring on any 1 day within the last 3 months. Other inclusion criteria were an IQ of $\geq$70 or mental age of at least 7 years. In keeping with the requirements of the local ethics committee, some evidence of cognitive impairment or psychosocial dysfunction was required to provide ethical justification for participation, specifically, that parents were sufficiently concerned about behavior/cognition to seek help. The protocol was approved by the ethics committee at all three study sites, and written informed consent was obtained from all parents and patients 16 years of age or older and oral agreement from patients younger than 16 years of age.

Patients were randomly assigned to receive lamotrigine (Lamictal, GlaxoWellcome, now GlaxoSmithKline, Stevenage, United Kingdom) followed by placebo, or placebo followed by lamotrigine, in addition to the current AED regime each for 13 weeks (Figure). 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 taking sodium valproate, lamotrigine was titrated up to 2 mg/kg per day ($\leq$12 years of age) or 150 mg/d (>12 years of age). For children not taking sodium valproate, lamotrigine was titrated up to 10 mg/kg per day ($\leq$12 years of age) or 300 mg/d (>12 years of age). During a 4-week, single-blinded 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.

At entry, physical and neurologic examination, history, routine and ambulatory EEG, standard biochemical tests, AED concentrations and IQ tests (Wechsler Intelligence Scale for Children, WISC-III) were performed and behavioral scales were completed by parents and teachers. Patients were assessed at the end of each treatment phase (weeks 17 and 31) when the following were recorded: physical examination, lamotrigine blood levels, ambulatory EEG, neuropsychologic 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 with the use of 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. A continuous run of epileptiform waveforms would be considered as one discharge if not interrupted by normal activity of more than 1 second. Discharges were considered subclinical when "the available methods of clinical observation, applied under particular circumstances, failed to show any changes in the patient."[8] Discharges were quantified in each patient during the eyes-open phase of a 12- to 24-hour period as frequency of discharges (number per hour) and discharge time (duration in seconds per hour). The minimum duration allocated to any single discharge was 1 second.

We assessed behavior with the Conners Rating Scales for parents and teachers. The Conners Rating Scales are factor analytically derived scales for assessing problem behavior in children. The parents' rating scale consists of a list of 93 questions and the teachers' rating scale of 39 questions. Raw scores are translated into *t* scores by sex and age. The *t* scores have a mean of 50 and a standard deviation of 10, and higher scores denote more serious behavior problems.[10] The parents' rating scale has 8 subscales designated as (I) antisocial, (II) anxious-shy, (III) conduct disorder, (IV) hyperactive-immature, (V) learning problem, (VI) obsessive-compulsive, (VII) psychosomatic, and (VIII) restless-disorganized. The teachers' rating scale has 6 subscales labeled as (I) anxious-passive, (II) asocial, (III) conduct problem, (IV) daydream-attention, (V) emotional-indulgence, and (VI) hyperactivity. Rating forms were completed by the same persons on all occasions.

The primary hypothesis tested was that behavioral scales would improve specifically in those patients who had a reduction of discharges during the active drug phase. Changes in global rating of behavior were analyzed by repeated-measurement multivariate analysis of variance (MANOVA) between treatment groups (lamotrigine and placebo), with response to lamotrigine as covariant (with or without reduction of discharges). To identify the most relevant behavioral subscale, the univariate test was used. A *P* value of <.05 was considered significant. All statistical tests were 2-tailed. Analysis was by intention to treat.

## RESULTS

Of the 64 patients screened, 61 were enrolled in the study and randomly assigned to receive first lamotrigine and