

## Add-on Lamotrigine in Pediatric Epilepsy in India

RAHUL JAIN, DEVENDRA MISHRA AND MONICA JUNEJA

*From the Department of Pediatrics, Maulana Azad Medical College (University of Delhi), Delhi 110002, India.*

*Correspondence to:*

*Dr Devendra Mishra,*

*Division of Pediatric Neurology,*

*Department of Pediatrics,*

*Maulana Azad Medical College,*

*2, Bahadur Shah Zafar Marg,*

*Delhi 110002, India.*

*drdmishra@gmail.com*

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Lamotrigine is a newer antiepileptic drug useful as oral adjunctive therapy in refractory epilepsy. Indian data on use of lamotrigine is limited. This study was conducted to evaluate add-on lamotrigine in Indian children with epilepsy. Twenty children (median age 90 months) receiving lamotrigine as add-on therapy for mean 26.7 (19.1) months, were followed for a median period of 7.9 (6-10) months. Follow-up was done every two weeks. The most common seizures types were either generalized tonic-clonic (6, 30%) or myoclonic (8, 40%). The average dose used was 3.86 mg/kg/day (with concomitant valproate). Good response (>50% reduction) or complete seizure control was seen in 72% patients. Side effects were seen in 27.5% patients and were 'mild' in more than half of these. Lamotrigine was stopped in two patients due to adverse reactions, which resolved on stopping the drug. Lamotrigine was observed to be an effective, add-on, broad-spectrum antiepileptic with 'mild' side effects in Indian children.

**Key words:** *Child, India, Intractable epilepsy, Lamotrigine, Newer antiepileptics.*

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Lamotrigine, a newer antiepileptic drug (AED), may be used add-on drug for both generalized and partial seizures, and also as the first-line drug for partial seizures [1,2]. The drug has shown to be effective for refractory partial and generalized seizures in children, with a low incidence of side-effects [3-5]. In India, the drug has been in clinical use since 2002, but scant data are available about the clinical use of lamotrigine in Indian children [6]. We ascertained the effectiveness and safety of lamotrigine as an add-on drug for epilepsy in Indian children.

### METHODS

The study was conducted from January to October 2009 at the Pediatric Neurology Clinic of a tertiary-care hospital attached to a medical college in North India. All children under 14 years (except one patient of 16 years), attending the Clinic and already receiving lamotrigine were retrospectively enrolled ( $n=14$ ), after written informed consent. Children

started on lamotrigine therapy between January to April 2009 were also enrolled prospectively ( $n=6$ ). Decision regarding starting lamotrigine in patients not responding to the first-line AEDs was taken by a clinician not directly involved with the study. All data were entered in a pre-tested structured proforma.

Neuroimaging (CT and/or MRI) and electroencephalography were available for most children. All children at the clinic undergo a comprehensive evaluation and management by a team consisting of developmental pediatricians, speech therapist, occupational- and physiotherapists, child psychologists and special educators. No additional investigations were done as part of the study.

Seizure type and frequency during the study were recorded using a seizure log filled by the parents or caretakers. Information about previous seizures was obtained from records available with the parents.

The doses of antiepileptic used were (mg/kg/day): carbamazepine, 10-30; clobazam, 0.1-2; clonazepam, 0.05-0.2; phenobarbitone, 3-8; phenytoin, 5-8; and, valproate, 10-60. The maintenance dose of lamotrigine used was between 1-6 mg/kg, once daily or in 2 divided doses with valproate, and 5-15 mg/kg daily given in 2 divided doses with enzyme-inducing AEDs (but not with valproate), with induction and dose changes as per standard guidelines [1]. Patients were followed prospectively for a period ranging from 6-10 months, on a two-weekly basis. Occasionally the OPD visits were earlier than two weeks if seizure control was inadequate, or child attended the casualty for breakthrough seizures. A structured proforma was designed to include details pertaining to diagnosis, age of onset of seizures, seizure type, frequency of seizures, nature and dose of first line antiepileptics. On follow up, details were obtained about change in seizure frequency, development of side effects and any modification done in the dose of lamotrigine to obtain seizure control or for addressing side-effects.

Therapeutic response was recorded as complete (100% seizure control), good (>50% seizure reduction), or none. Enquiry was made about the following side effects for all patients during the study period and reviewed retrospectively from the case-records: skin rashes (including severe skin reactions like Stevens-Johnson syndrome and toxic epidermal necrolysis) with or without fever, malaise, flu-like symptoms, drowsiness, lymphadenopathy and facial edema [1]. Others known adverse events like angioedema and photosensitivity; diplopia, blurred vision, and conjunctivitis; and dizziness, drowsiness, insomnia, headache, ataxia, nystagmus, tremor, tiredness, nausea and vomiting, irritability and aggression, hallucinations, agitation, and confusion, were also assessed [1]. The side effects were categorized as '*mild*' if they were not spontaneously reported by the parent and were only elicited on enquiry. Side effects were *moderate*, if parents spontaneously reported the side effect, as a complaint developing after initiation of lamotrigine but the symptom was not interfering with the child's daily activity. Side effects were *severe* if the parent spontaneously reported it and asked for withdrawal of the drug as it was interfering with the child's daily

activity [7]. All patients came regularly for follow-up during the study period.

## RESULTS

Twenty patients received add-on lamotrigine during the study period (17 males). Fourteen children were already on lamotrigine at the time of starting the study and six were started during the study period. The clinical profile is shown in **Table I**. Lennox Gastaut syndrome and West syndrome were diagnosed in 1 case each. Neurological co-morbidities were present in 14 cases. The deficits included mental retardation in 12, cerebral palsy in four, autism in three, and vision deficit in two children.

The median age of onset of seizures was 10.5 months (range, 1 month-9yr 5 months). All the cases had previously been tried on at least two appropriate AEDs and had seizure frequency of at least one per month at the time of starting lamotrigine. There were two types of seizures in six children. All children were on sodium valproate and six were additionally on clobazam at the time of starting lamotrigine. The drugs previously tried in these patients included phenytoin, carbamazepine, phenobarbitone,

**TABLE I** CLINICAL PROFILE OF STUDY CHILDREN (N=20)

Characteristic	No
Age, median (range), mo	90 (29-199)
Duration of LTG therapy, mean (SD)*, mo	26.7 (19.1)
Median follow up (range), mo*	7.9 (6-10)
Predominant seizure type	
GTCS	6
Atonic	1
Myoclonic	8
Absence	1
Partial	4
Etiologic diagnosis	
Idiopathic	4
Remote symptomatic	10
Cryptogenic	6
AEDs used before LTG, median (range)	3 (2-4)
Concomitant AEDs used, median (range)	2 (1-3)

AED: antiepileptic drug; LTG: lamotrigine; \*n=18.

clonazepam and clobazam. The mean dose of lamotrigine used in the cases was 3.86 mg/kg/day (excluding those in which the drug was withdrawn due to adverse effects). Neuroimaging was available for 18 patients and showed some abnormality in 12 cases (sequelae of birth asphyxia 5, sequelae of tubercular meningoencephalitis 2, diffuse cerebral atrophy 2, cerebral malformation 2, and focal gliosis 1). Interictal-EEG was available in only 16 cases and was abnormal in fourteen.

**Efficacy:** In two children, lamotrigine was withdrawn due to adverse effects and these cases were excluded from further analysis. Overall, 44.4% cases had good response with >50% reduction in seizure frequency and 27.7 % becoming seizure free (**Table II**). The response was good in all type of seizures except myoclonic seizures. None of the patients with myoclonic seizures became seizure free on lamotrigine. Lamotrigine was withdrawn in three patients with myoclonic seizures, due to non response in two and due to adverse effects in one.

Overall, lamotrigine was withdrawn in 6 patients during the study period, 2 due to adverse effects and 4 due to non-response. In patients with two types of seizures, > 50% reduction in other seizure types was seen in four out of six cases. Worsening of seizures was not observed in any child.

**Adverse effects:** Adverse effects were observed in five children and all occurred within first three months of starting lamotrigine. Drug was withdrawn in one child due to rash and in another due to severe

emotional lability and agitation. In both these cases, symptoms subsided promptly on withdrawal of the drug. The side effects noted in other three cases were anorexia in one, and drowsiness and agitation in two. These were transient in nature.

**DISCUSSION**

This observational follow-up study in Indian children showed lamotrigine to be safe and efficacious second line anti-epileptic drug for pediatric epilepsy resistant to first-line AEDs. Good response was seen in generalized tonic-clonic, atonic, absence and partial seizure types, whereas modest response was observed in myoclonic seizures. Serious side effects were infrequent and responded promptly to drug withdrawal.

Studies from other countries have also shown lamotrigine to be effective as add-on therapy in children with refractory epilepsy [3,4,8-10]. In a multicentric study on 285 children with treatment resistant epilepsy, one-third patient had 50% or more reduction in seizure frequency on lamotrigine. Response was good in all seizure types, particularly in absence and atonic seizures [8]. In another study on 120 children with intractable epilepsy, 9.4% patients became seizure free and 29% patients showed improvement after 3-month treatment with lamotrigine [9]. Studies have also shown improvement in academic and social functioning of the treated cases [10], which could be due to improved seizure control. Others have also reported comparable responder rates and side effect incidence with lamotrigine among Asian children with intractable epilepsy [4,5].

The poorer response of myoclonic seizures to lamotrigine has also been seen by others. In various studies, only 0-30% patients with myoclonic seizures responded to lamotrigine, although the number of cases with myoclonic seizures was small in these studies [8,11,12]. Worsening of seizures with LTG has previously been reported in patients with severe myoclonic epilepsy of infancy [13].

The drugs commonly used at our clinic are the first-line drugs (phenytoin, phenobarbitone, carbamazepine, valproate and clonazepam) because these are provided free-of-charge to the patients, most of

**TABLE II** EFFICACY OF LAMOTRIGINE BY PREDOMINANT SEIZURE TYPE (N=18)

Seizure type	Poor/no response No. (%)	Good response No. (%)	Seizure free No. (%)
GTCS (n=5)	1 (20)	1 (20)	3 (60)
Atonic (n=1)	–	1 (100)	–
Myoclonic (n=7)	4 (57.1)	3 (42.8)	–
Absence (n=1)	–	–	1(100)
Partial (n=4)	–	3 (75)	1 (25)
Total	5 (27.7)	8 (44.4)	5 (27.9)

Poor/no response: <50% reduction; Good response: 50-99% reduction.

### WHAT THIS STUDY ADDS ?

- Lamotrigine is a safe and efficacious add-on anti-epileptic in Indian children with all forms of seizures, except myoclonic seizures.

whom belong to lower or lower-middle classes. Thus, despite the indications for newer AEDs in some patients, these can not be routinely prescribed as the patients are unable to afford the same. Therefore, one of the major limitations of this study was the small sample size. In addition, there was no predetermined objective criterion for starting lamotrigine, and it was based on the treating clinicians' decision. The strengths of the study were the long follow-up, complete data for all patients, and frequent review of the patients for adverse effects and efficacy.

To conclude, our study showed that lamotrigine has infrequent side effects, and good efficacy as an add-on AED, with >50% responder rate in all type of seizures, except myoclonic seizures. It is indicated as adjunctive therapy for partial seizures, primary generalized tonic-clonic seizures, and the generalized seizures of Lennox-Gastaut syndrome in children ( $\geq 2$  years of age) with epilepsy in India, although its high cost will preclude widespread use in low-resource settings.

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