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# Efficacy and tolerability of lamotrigine in Juvenile Myoclonic Epilepsy in adults: A prospective, unblinded randomized controlled trial

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ABSTRACT

*Purpose:* Controlled randomized studies recommending the clinical use of lamotrigine in adult populations with the diagnosis of Juvenile Myoclonic Epilepsy are still lacking. To compare the efficacy and tolerability of lamotrigine versus valproate in adult patients with JME.
*Methods:* This was a prospective, randomized, controlled, pragmatic, long-term and open-label treatment trial. Patients were randomized to use valproate or lamotrigine. The primary end points of the study were: (1) time from randomization to treatment failure (withdrawal); (2) time from randomization to seizures remission. Secondary ending points were: (1) frequency of clinically important adverse events and (2) change in the QOLIE-31 after randomization. The definition of seizure remission was based on disappearance of all seizure types and EEG discharges.
*Results:* We found that the time to withdraw treatment after randomization was not significantly different in lamotrigine and valproate groups. Long-term seizures freedom was equal in the both groups of the trial; only 8 (19.1%) patients randomized to lamotrigine and 6 (19.4%) randomized to valproate were not seizure free after 4 months of treatment. Between 17.03% (lamotrigine) and 35.3% (valproate) of patients reported adverse reactions at some point in the intention-to treat study ($p = 0.07$). All subscales of the QOLIE-31 questionnaire, except that related to side effects of medication, improved more than 5 points with respect to baseline period in both groups
*Conclusion:* Lamotrigine is effective in adult patients with Juvenile Myoclonic Epilepsy and better tolerated than valproate, although the incidence of idiosyncratic reactions could be a cause of concern.


## 1. Introduction

Juvenile Myoclonic Epilepsy (JME) represents the most common form of idiopathic generalized epilepsy (IGE).[1]

JME seizures respond well to antiepileptic drugs (AEDs), particularly valproate. The SANAD (Standard and New Antiepileptic Drugs) study reported that valproate was the most effective and best-tolerated first-line AED for patients with IGE, including JME, when it was compared to lamotrigine and topiramate (TPM).[2]

Valproate is the first-line drug in men with JME, but in female population, lamotrigine (LTG) is preferred due to the teratogenic and endocrinologic side effects such as polycystic ovary syndrome and weight-gain associated to valproate. Recent data suggest that it may soon be used as first line treatment[2–5]; nevertheless, some studies have reported aggravation of JME with LTG.[6–12]

LTG is a phenyltriazine derivative which acts through inhibition of voltage-activated sodium channels and possibly calcium channels, preventing the release of glutamate.[5] LTG is effective in controlling generalized tonic–clonic seizures (GTCS) and absence seizures[13–17]; while there are some reports of myoclonic seizure exacerbation.[6,7] Nevertheless, many studies performed over the recent years have demonstrated the clinical utility of this AED for the treatment of JME.[6–9]

Demonstration of LTG's usefulness in JME is especially important for women who live in developing countries, due to the lack of levetiracetam, zonisamide and TPM[18–20] and also for those female or male patients who have had adverse reactions to valproate or who have contraindications for its use.

That's why, in some scenarios, LTG has become the first line AED in women with JME of childbearing potential and even in men. Nevertheless, to our knowledge, open labeled, prospective, controlled randomized trials, that allow recommendation of LTG for adult population with JME in clinical practice, are still lacking.

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We carried out the present trial to determine the efficacy and tolerability of lamotrigine in adult patients with JME.

## 2. Methods

### 2.1. Study design

This was a prospective, randomized, controlled, pragmatic, long-term, open-labeled treatment trial. The study was carried out at the National Institute of Neurology and Neurosurgery in Havana, Cuba.

### 2.2. Study population

Patients from the whole country are referred to our institution which is a tertiary center. The epilepsy section offers medical assistance to 1089 patients with epilepsy. Juvenile Myoclonic Epilepsy represents approximately 10.3% of all epileptic syndromes treated in our institution.

### 2.3. Diagnosing process and follow-up

All subjects were enrolled in the study sequentially from the outpatient clinic. The first patient was included on January 2nd 2008, and randomization continued up to June 30th 2010. Attempts were made to follow all patients for at least 2 years, but those who did not return to the outpatient clinic, were included in until the moment they were evaluated for the last time (ITT protocol). Trial design can be seen in Fig. 1.

All patients and two of their relatives were interviewed by experienced epileptologists concerning seizure types, age at seizure onset, seizure precipitant factors, possible circadian rhythm of seizures and previously used medications.

In all the patients where Juvenile Myoclonic Epilepsy was suspected, a routine 21-channel EEG was obtained, according to the international 10–20 system employing a Medicid EEG digital machine, at the moment of entering the study and after 2 years of follow-up. All patients were sleep deprived the night before to EEG performance. At least 10 min of sleep were recorded in each patient, which primarily resulted in early sleep stages recording (stages 1 and 2 of non-REM sleep) and only rarely stage 3 non-REM sleep was seen. EEG recordings had a mean duration of approximately 30 min.

Taking into account seizure semiology and the electrographic pattern obtained, the diagnosis of JME was made by two epileptologists according to the ILAE criteria.[13] Seventy-two patients (100%) had myoclonic seizures, 45 patients had GTCS (62.5%) and absence seizures were reported in only 27 (37.5%).

### 2.4. Inclusion criteria

Patients were included in the study if they had past history of two or more generalized myoclonic seizures. Tonic–clonic or absence seizures in the previous years were also taken into

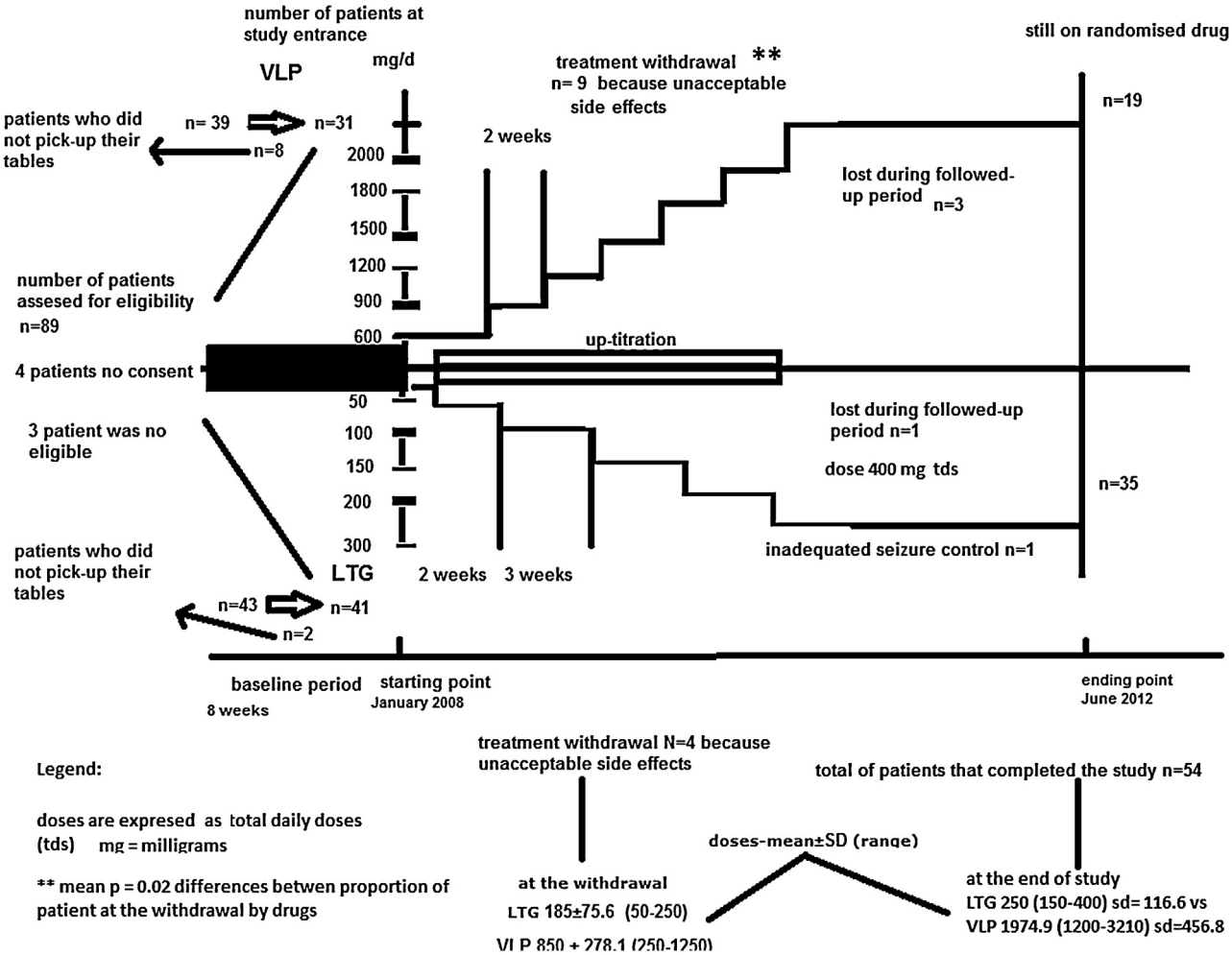


**Fig. 1.** Trail profile. The total number of patients that withdrew from treatment for any reason was 12/31 in the valproate group and 6/41 in the lamotrigine group (differences between two proportions), $p = 0.02$.