

**Levetiracetam Versus Valproate in Idiopathic  
Generalized Tonic-clonic Seizures**

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## Study protocol

This study was a non-randomized open label active-controlled clinical trial with a two-parallel-group design aimed to compare efficacy of levetiracetam (LEV) with valproate (VPA) for treatment of patients with idiopathic (genetic) generalized epilepsy. Patients aged  $\geq 16$  years with diagnosis of genetic generalized tonic-clonic seizures only (GTCS) or juvenile myoclonic epilepsy (JME) who were referred to our tertiary University hospital and epilepsy clinic were included. Normal brain magnetic resonance imaging (MRI), lack of focal epileptic discharges with or without generalized epileptiform discharges in electroencephalography (EEG) and seizure symptomatology in favor of GTCS or JME were mandatory. Patients with history of hepatic, renal and hematologic disorders, known psychosis, psychogenic non-epileptic seizure, status epilepticus and illegal drug abuse, patients who had been treated with LEV or VPA in the last 6 months and those with poor adherence to medications or plan for pregnancy were excluded. The study was approved by University ethics committee and performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before participation.

Patients were treated by LEV or VPA. LEV was started with 500 mg/day (twice daily as equal doses) and the dose was increased by 500 mg/week to a total dose of 2000 mg/day if needed. Starting dose for VPA was 500 mg/day with 500 mg/week increase to the maximum dose of 1500 mg/day in two divided doses based on clinician's decision. Patients, who experienced adverse events (AEs) during titration which could be ameliorated by dose reduction, were reverted to previous acceptable dose. If one episode of seizure occurred, doses were increased to maximum 3000 mg/day for LEV and 2000 mg/day for VPA with the same titration protocol, according to clinician's judgment. Evaluations were scheduled at weeks 4, 12 and 26 after initiation of treatment. In each visit by neurologist, adherence to AED, seizure recurrence and AEs were assessed. The primary outcomes were time to first seizure and seizure freedom rate at 6 months after start of treatment. The secondary outcomes were defined as time to withdrawal and withdrawal rate at 6th month and also severity of adverse events. Withdrawal rate was calculated based on discontinuation of monotherapy with each medication due to AEs, lack of efficacy and need to drug switch or combination therapy.

## **Statistical analysis**

SPSS version 19 software (SPSS Inc.) was used for statistical analysis. Chi-square test or Fisher's exact test were used to compare categorical variables between groups. Numerical variables were analyzed with student's t-test or Mann-Whitney test, according to distribution. Time to first seizure and time to withdrawal were analyzed using the Kaplan–Meier survival curves. For analysis of time to first seizure, patients who did not experience any seizure during the first 26 weeks of treatment were censored at the end of 26 weeks. For analysis of time to withdrawal, patients who discontinued medication before 26 weeks were considered to have the event. Cox's regression model was used to investigate time to withdrawal and time to first seizure. A Hazard ratio (HR) of less than 1 was considered in favor of LEV. P-value of less than 0.05 was considered statistically significant.