

Levetiracetam: preliminary efficacy in generalized seizures

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ABSTRACT – Levetiracetam is a novel antiepileptic drug (AED) with proven efficacy against partial seizures, but there is limited information about its effectiveness against generalized seizures. In animal models, levetiracetam protects against seizures in audiogenic susceptible rodents, and it is effective in the Genetic Absence Epilepsy Rat from Strasbourg, a model of absence seizures. In these models, levetiracetam has a therapeutic index that is higher than those of other AEDs. A number of small open-label studies suggest that levetiracetam reduces seizure frequency in patients with generalized seizures, including primarily generalized seizures and myoclonic seizures. Case reports provide additional information regarding the potential efficacy of levetiracetam in postanoxic, post-encephalitic and progressive myoclonus. Although randomized controlled studies of patients with generalized seizures have not yet been conducted, on the basis of available information, levetiracetam may be promising in the treatment of generalized seizures.

KEY WORDS: Levetiracetam, generalized seizures, myoclonic seizures, absence seizures

Introduction

Epileptic seizures are classified by clinical semiology and ictal and interictal EEG findings as partial or generalized according to the system proposed in 1981 by the International League Against Epilepsy (ILAE; *table 1*) [1]. Partial seizures include simple partial, complex partial, and secondarily generalized, whereas generalized seizures include absence, myoclonic, clonic, tonic, tonic-clonic and atonic seizures. The distinction between partial and generalized seizures is generally based on whether the initial clinical and EEG changes are limited to one cerebral hemisphere (partial) or involve both hemispheres (generalized).

In 1989, a revised classification of epilepsies and epileptic syndromes was

proposed by the ILAE [2]. It referred to partial seizures as localization-related, and indicated that temporal, frontal, parietal, and occipital lobe epilepsies may involve both partial and secondarily generalized seizures. It further grouped localization-related and generalized epilepsies as idiopathic (no underlying cause), symptomatic (consequence of a known or suspected CNS disorder), and cryptogenic (hidden or occult cause). Generalized idiopathic forms include childhood absence epilepsy and juvenile myoclonic epilepsy, whereas Lennox-Gastaut syndrome and myoclonic absence epilepsy are examples of syndromes involving generalized seizures that may be cryptogenic or symptomatic.

In many cases, the ictal and interictal EEG findings do not correlate with

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Table 1. Types and characteristics of seizures [1, 5]

Seizure type	Clinical features	EEG features
IA. Simple partial (focal)	Consciousness not impaired; may occur with motor, somatosensory, autonomic, or psychic signs or symptoms depending on location of electric discharge	Local contralateral electrical discharge starting over area of cortical representation
IB. Complex partial	Consciousness impaired; may begin with simple symptomatology or occur without warning; automatisms may be present	Unilateral or often bilateral electrical discharge; may be diffuse or focal in temporal or frontotemporal regions
IC. Secondarily generalized	May begin as either simple or complex partial seizure and then evolve to generalized seizure with loss of consciousness; may occur with tonic, clonic, or tonic-clonic components	Evolve from simple to generalized features
IIA. Absence seizure	Brief loss of consciousness that may occur alone or with mild clonic, atonic, tonic, or autonomic components or with automatisms	Regular and symmetric spike-wave patterns of 3 Hz (may be 2-4 Hz); bilateral abnormalities
IIB. Myoclonic seizure	Single or multiple myoclonic jerks	Polyspike-wave pattern; sometimes spike-wave or sharp and slow-wave pattern
IIC. Primarily generalized	Loss of consciousness may occur without warning or preceded by myoclonic jerks; may occur with tonic, clonic, or tonic-clonic components	Fast activity (10 Hz) and slow waves; occasional spike-wave patterns during clonic phase; decreasing frequency and increasing amplitude during tonic phase

clinical semiology. As a result, a classification system based solely on ictal semiology has been proposed [3]. This system classifies seizures into five groups: auras, autonomic seizures, dialeptic seizures, motor seizures, and special seizures. For example, dialeptic seizures include an alteration of consciousness with complete or at least partial amnesia for the episode, whereas motor seizures have motor signs as the main clinical symptomatology. The terms axial, bilateral asymmetric, and generalized are used to further characterize the clinical semiology. Axial refers to manifestations involving the muscles of the trunk and proximal extremities; bilateral asymmetric indicates that the symptoms have a bilateral distribution but are suggestive of a focal seizure; and generalized refers to widespread and equal involvement of both hemispheres and the distal and proximal segments.

Recently, an ILAE task force proposed classifying seizures according to a diagnostic scheme based on ictal phenomenology, seizure type, syndrome, etiology, and degree of impairment [4]. According to this scheme, seizures are divided into self-limiting and continuous seizures, and further subdivided into generalized and focal seizures. The term focal is used in place of partial to clarify that these seizures arise in part of one hemisphere rather than as part of a syndrome. Some types of self-limiting focal and generalized seizures are listed in *table 2*.

Regardless of which system is used to classify seizures, the term generalized refers to seizures affecting both hemispheres of the brain. The symptoms and EEG findings associated with generalized seizures vary depending on the type (*table 1*). Generalized seizures may begin with myoclonic jerks and subsequently cause either an alter-

ation of consciousness, tonic or clonic movements, or both [5]. For example, absence seizures typically involve a brief impairment of consciousness, which may occur with changes in muscle tone, automatisms, or mild clonic movements. Generalized seizures may occur without any warning signs. They may involve tongue biting, incontinence, automatic behavior, and postictal behavior.

Table 2. Self-limited epileptic seizure types defined in 2001 ILAE Task Force proposal [4]

Generalized seizures	Focal seizures
<ul style="list-style-type: none"> • Tonic-clonic (may begin with clonic or myoclonic phase) • Clonic (with or without tonic features) • Typical absence seizures • Atypical absence seizures • Myoclonic absence seizures • Tonic seizures • Spasms • Myoclonic seizures • Eyelid myoclonia (with or without absences) • Myoclonic atonic seizures • Negative myoclonus • Atonic seizures • Reflex seizures in generalized epilepsy syndromes 	<ul style="list-style-type: none"> • Focal sensory seizures (with elementary or experiential sensory symptoms) • Focal motor seizures (with elementary clonic motor signs; asymmetric tonic motor seizures; typical temporal lobe automatisms; hyperkinetic automatisms; focal negative myoclonus; or inhibitory motor seizures) • Gelastic seizures • Hemiconic seizures • Secondarily generalized seizures • Reflex seizures in focal epilepsy syndromes

It is sometimes difficult to distinguish between focal and generalized seizures in individual patients. For example, both absence seizures and complex partial (focal) seizures occur with loss of consciousness and may be accompanied by automatic behaviors [5]. Likewise, primarily and secondarily generalized seizures have similar clinical features that may only differ in their onset. This underscores the utility of antiepileptic agents that have proven broad-spectrum activity against both focal and generalized seizure types. Valproate and lamotrigine are examples of this. Levetiracetam is a novel antiepileptic drug (AED) with proven efficacy against partial seizures [6-8], but there is limited information about its effectiveness against generalized seizures. This article will review available clinical information that suggests levetiracetam is a broad-spectrum AED that may be effective in treating generalized seizures.

Preclinical findings with levetiracetam

The mechanism by which levetiracetam provides protection against seizures is not fully known, but it does not appear to include a direct interaction with conventional AED drug targets [9]. Instead, it appears to involve inhibition of N-type Ca^{2+} channels and reversal of the inhibition by zinc on both GABA and strychnine-sensitive glycine currents [10]. In preclinical studies, levetiracetam protected against audiogenic seizures in mice in a dose-dependent manner, with activity against both tonic and clonic convulsions and wild running behavior [11]. This profile was similar to that of clonazepam and sodium valproate but differed from phenytoin and carbamazepine, which were more effective against tonic than clonic convulsions. Notably, when an ED_{25} dose of levetiracetam (5.5 mg/kg i.p.) was evaluated in combination with valproate, clonazepam, phenobarbital, carbamazepine, or phenytoin in audiogenic susceptible mice, it markedly increased the anticonvulsant potency of these AEDs without affecting their adverse event potential or their concentrations in plasma and brain [12]. Levetiracetam also protected against tonic seizures and wild running behavior in audiogenic-susceptible Wistar rats [13]. In the Genetic Absence Epilepsy Rat from Strasbourg (GAERS), a model with EEG and spike-and-wave discharges characteristic of absence seizures [14], levetiracetam markedly suppressed spike-and-wave discharge, while leaving the underlying EEG trace in a normal awake state [13].

In rodent models, levetiracetam has a profile different from other AEDs [15, 16]. Levetiracetam provided selective, potent protection against generalized epileptic seizures in electrically and pentylenetetrazol-kindled mice while lacking anticonvulsant activity in the acute maximal electroshock seizure and maximal pentylenetetrazol seizure tests in mice [15]. In the same study, most other AEDs were

protective in both the acute seizure tests and kindling models. Levetiracetam also differed from other drugs in various chemoconvulsive seizure tests, where it provided protection against secondarily generalized activity induced by pilocarpine in mice and pilocarpine and kainic acid in rats but lacked activity against clonic convulsions induced by bicuculline, picrotoxin, 3-mercapto-propionic acid, 4-aminopyridine, and caffeine [15].

The therapeutic index for levetiracetam based on the ratio of seizure suppression in GAERS rats relative to impairments in rotarod performance was 235. In the same study, the safety ratios of valproate and ethosuximide, commonly used in absence epilepsy, were 2 and 5, respectively, in GAERS [15, 16].

Levetiracetam was further distinguished from valproate, clonazepam, and carbamazepine on the basis of evoked responses in the highly seizure-prone CA3 area of rat hippocampal slices [17]. When these slices were perfused with a high potassium, low calcium fluid, the field potential evoked by constant-current fimbrial stimulation became increasingly epileptiform with population spikes of greater amplitude and more repetitive in number. At clinically relevant concentrations, levetiracetam (32-100 μM) opposed the increase in the amplitude of the first population spike, consistently reduced higher-order population spikes, and reduced the number of repetitive spikes per evoked response. In the same study, valproate (1 mM), clonazepam (1 μM), and carbamazepine (50 μM) decreased the number of repetitive spikes, and only valproate showed a trend for inhibiting the amplitudes of the higher-order population spikes. This study suggests that levetiracetam is distinguished from other AEDs by its ability to antagonize neuronal hypersynchrony in the seizure-prone CA3 area of the rat hippocampus.

Open-label, prospective, follow-up, and postmarketing studies

Adolescents and adults

Levetiracetam was shown to have a beneficial effect in a group of 12 adolescent and adult patients who were photosensitive; 11 of them had generalized epilepsy (tonic-clonic seizures, but mainly absences and myoclonic seizures) [18]. Single oral doses of levetiracetam suppressed generalized EEG responses to intermittent photic stimulation (IPS) in two of the five patients receiving 250 or 500 mg, and it abolished the response in all six patients receiving doses of 750 or 1000 mg. The effect of levetiracetam appeared to be dose-related, occurred at peak plasma levels, and lasted for 6 to 30 hours. Notably, two patients reported spontaneously a clear reduction of myoclonus after levetiracetam. One of these patients had a history of daily visually-induced myoclonic jerks and was titrated to levetiracetam 1000 mg on the basis of the IPS

Table 3. Characteristics of five patients with idiopathic generalized epilepsies

Patient	Sex	Age	Seizure type 1	Seizure type 2	EEG	Epileptic syndrome	Previous AEDs	Levetiracetam monotherapy	Follow-up	Seizure control	EEG	Sensitivity to IPS (PPRs)
1	F	26	Myoclonic	Primarily generalized	Polyspike waves	Juvenile myoclonic	None	1 g	8 mo	Yes	Normal	
2	F	15	Eyelid myoclonia	Primarily generalized	Generalized spike-waves, PPRs	Eyelid myoclonia with absences	None	2 g	4mo	Reduced	Generalized spike-waves, PPRs	Reduced
3	F	21	Eyelid myoclonia	Primarily generalized	Generalized spike-waves, PPRs	Eyelid myoclonia with absences	Yes	1 g	4 mo	Yes	Normal	Abolished
4	F	14	Myoclonic	Primarily generalized	Polyspike waves, PPRs	Juvenile myoclonic	Yes	2 g	5 mo	Yes	Normal	Reduced
5	F	37	Primarily generalized	None	PPRs	Pure visual sensitive epilepsy	Yes	2 g	4 mo	Yes	Normal	Reduced

IPS = intermittent photic stimulation; PPR = photoparoxysmal response.

response. She subsequently used levetiracetam 500 mg bid for 3 years and had full control of her myoclonic jerks [18].

The effect of levetiracetam in myoclonus was assessed in a pilot study of eight patients who had not experienced sufficient improvement after at least one standard medication for myoclonus [19]. Patients remained on stable doses of current medications and then received levetiracetam. The dose was titrated over 4 weeks from 500 mg per day to 1000 mg bid, and then held constant at this level for an additional 4 weeks. Seven of the eight patients completed the trial; the other patient developed sedation, nausea, and irritability during dose titration and withdrew after 2 weeks. Seizures did not occur during the trial. Three patients with cortical myoclonus had meaningful reductions in myoclonus scores on the Unified Myoclonus Rating Scale after levetiracetam treatment [19].

A retrospective review of case records identified 13 patients with resistant juvenile myoclonic epilepsy who had participated in various open-label trials of levetiracetam since 1995 [20]. All of these patients were followed for at least 1 year after initial add-on dose titration with levetiracetam, and on average, they were also receiving three other AEDs. After treatment with levetiracetam at doses of 2000 to 4000 mg per day for 22 to 50 months, 12 (92%) patients had reductions in seizure frequency of 50% or more, and six (46%) patients became seizure-free.

Postmarketing experience supports the antimyoclonic properties of levetiracetam. Levetiracetam was administered without titration at 4000 mg per day (for 16 days) to a patient with post-anoxic myoclonus and to two patients with Unverricht-Lundborg disease, a progressive myoclonus epilepsy caused by mutation of the gene encoding cystatin B (for 14 days and 14 weeks, respectively) [21]. In all three patients, levetiracetam produced a clear improvement of myoclonus without any side effects. Two patients

were switched subsequently to piracetam, which appeared somewhat less effective, whereas the third patient returned to her prior state following discontinuation of levetiracetam. In another group of three case reports, levetiracetam 500 to 750 mg bid (over 8 weeks, 5 weeks, and for an unknown period) provided substantial improvement in three patients with posthypoxic and postencephalitic myoclonus [22]. The patient with the best response had been unable to eat independently or walk without falling. Within 24 hours of starting levetiracetam, her myoclonus subsided markedly, allowing her to drink from an uncovered cup without spilling and to do housework for the first time in 10 years.

The characteristics of five patients with idiopathic generalized epilepsies who were treated with levetiracetam monotherapy are summarized in *table 3*. One of these patients (No. 1), born in 1976, presented at the age of 21 years with frequent early morning myoclonic jerks. At the age of 23, she experienced a tonic-clonic seizure. Three years later, she was admitted to the neurological department in Strasbourg (France) with a second primarily generalized tonic-clonic seizure. Her CT scans were normal. The EEG showed generalized polyspike and wave discharges (*figure 1*). She was treated with levetiracetam monotherapy 500 mg for 15 days, then 1000 mg/day. Since receiving levetiracetam (with 8 months of follow-up), the patient has reported a complete disappearance of early morning myoclonia. Both the sleep and wake-up EEG were free of generalized discharges.

A 12- to 16-week safety study of levetiracetam involving 219 patients with refractory seizures included 37 patients with primarily generalized seizures (tonic-clonic, myoclonic, and absence seizures). Of these 37 patients, approximately one-half had seizure reductions of 50% or more, and 8% were seizure-free during the entire treatment period [23].

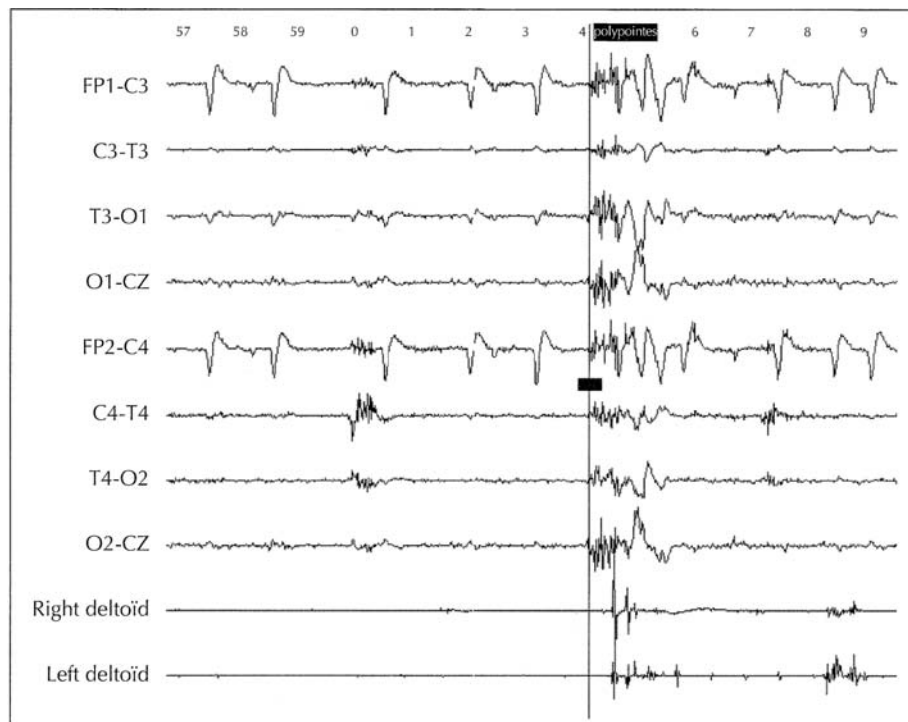


Fig. 1. Patient No. 1. Awake EEG demonstrates polyspikes and waves accompanied by myoclonia.

Thirty-six adults with drug-resistant generalized epilepsy received levetiracetam at Johns Hopkins University and Vanderbilt [24]. All patients had failed treatment with at least two other AEDs and had a baseline seizure frequency of more than one per month. This group included 27 (75%) patients with idiopathic generalized seizures and nine (25%) with symptomatic/cryptogenic generalized seizures. Overall, 75% (27/36) of patients achieved reductions in seizure frequency of more than 50%, and 42% (15/36) became seizure-free. Seven (19%) patients achieved monotherapy with levetiracetam. The median daily dose of levetiracetam was 1620 mg (range, 500 to 4000 mg). Three (8%) patients discontinued levetiracetam due to adverse events, including two patients with mood disorders.

Children

A retrospective review of children with refractory generalized epilepsies identified 16 who had been treated with levetiracetam for 4 weeks or longer [25]. These children averaged 10.3 years of age and included 11 with Lennox-Gastaut syndrome, two with myoclonic-astatic epilepsy, two with childhood absence epilepsy, and one with myoclonic epilepsy. These patients received levetiracetam for a mean duration of 2.5 months (range, 1 to 6 months) at a mean dose of 29 mg/kg/day (range, 15 to 52 mg/kg/day). Concomitant treatment included lamotrigine (10 patients), topiramate (six patients), valproate (five patients), zonisamide (three patients), and vagal nerve stimulation

(two patients). Levetiracetam reduced seizure frequency by more than 50% in 10 (63%) patients and by more than 75% in six (38%) patients. Three (19%) patients became seizure-free, including one patient each with absence, myoclonic, and myoclonic-astatic epilepsy. Levetiracetam was well tolerated; side effects were uncommon and generally mild. Behavioral changes were reported in three children, decreased appetite in two children, and asthenia in one child. However, none of the children discontinued levetiracetam due to a side effect.

Double-blind studies

To date no double-blind randomized controlled trials designed specifically to evaluate levetiracetam in patients with generalized seizures have been published. However, in one study the percentage reduction in seizure frequency in patients with generalized seizures was similar to that reported for partial seizures [26].

Discussion

Levetiracetam has a profile in animal seizure models that differs from other AEDs [14, 15], and studies in seizure-prone rat hippocampal slices show that it possesses the unique ability to antagonize neuronal hypersynchronization [17]. Moreover, the activity seen in audiogenic sei-

zure models whether administered alone or in combination with other AEDs, and its activity in the GAERS model of absence seizures, predict that levetiracetam may have good efficacy in patients with generalized seizures [11-13].

Clinical experience in open-label studies and anecdotal case reports suggest that levetiracetam may be effective in the treatment of several forms of generalized seizures in adults and children, including myoclonic, absence, and primarily generalized seizures.

Although available information suggests that levetiracetam may be effective in generalized seizures, prospective randomized clinical studies are still required to determine which seizure subtypes will respond best to therapy. Currently, multicenter controlled clinical trials of levetiracetam for tonic-clonic and myoclonic seizures are being conducted in patients with juvenile myoclonic epilepsy. It is hoped that further studies will provide additional information as to the preferred dosing regimen for children and adults with various types of generalized seizures.

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