

Levetiracetam-induced myoclonic status epilepticus in myoclonic-astatic epilepsy: a case report

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ABSTRACT – We report on a 3-year-old boy with myoclonic-astatic epilepsy who developed myoclonic status epilepticus with continuous twitching of the face and unresponsiveness under monotherapy with levetiracetam. Recently, a nonconvulsive status epilepticus in an adult epilepsy patient has also been described. Our observation points to the possibility of a causal relationship between the induction of myoclonic status by levetiracetam in certain patients with Doose's syndrome. However, a spontaneous evolution cannot be excluded. Levetiracetam is a well-known drug for the control of myoclonic seizures. A controlled study would provide a better understanding of any possible aggravating role in certain forms of myoclonic-astatic epilepsy.

Key words: levetiracetam, myoclonic status epilepticus, myoclonic-astatic epilepsy, Doose's syndrome, aggravating effect of AEDs

Levetiracetam is a newer-generation, anti-epileptic drug (AED) with a favourable pharmacokinetic profile, minimal plasma protein-binding and a low incidence of adverse effects and interactions with other AEDs (Sander *et al.* 2001, Perucca and Johannessen 2003). In adults, its efficacy has been shown in epilepsies with both, generalized and partial seizures. Furthermore, there is evidence of an anti-myoclonic effect in adults (Genton and Gelisse 2000, Gelisse *et al.* 2003, Di Bonaventura *et al.* 2005). Because of its properties, LEV offers, in theory, an interesting alternative for the treatment of childhood epilepsy syndromes with myoclonic seizures.

There are however, anecdotal reports that LEV may increase seizure fre-

quency in patients with refractory epilepsy (Bird and Jospheph 2003, Nakken *et al.* 2003) or induce convulsive or non-convulsive status epilepticus (Nakken *et al.* 2003, Atefy and Tettensborn 2005). We report on a 3-year-old boy with myoclonic astatic epilepsy (MAE) or Doose's syndrome, who developed myoclonic status epilepticus with continuous twitching of the face and unresponsiveness under monotherapy with levetiracetam at a dose of 30 mg/kgbw/d. This is the first description of myoclonic status induced by LEV in a child with MAE.

Case report

The patient is the second of three children of non-consanguineous, Swiss-

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Hungarian parents. His mother suffered from two febrile seizures in early childhood. There was an uneventful pregnancy and birth, and, so far, normal development. A first tonic-clonic seizure lasting three minutes occurred at the age of three. Interictal EEG showed normal background activity during wakefulness, generalized spike-waves appeared only during sleep. A few weeks later, myoclonic seizures (brief jerks of the shoulders) were observed for the first time. In the following weeks they became more frequent, occurred in short series and on one occasion, while the boy was playing computer-games, showed evolution to a tonic-clonic seizure. Anti-convulsive treatment with valproic acid (VPA) was started. A few days after reaching a dose of VPA 30 mg/kgbw/d, there was a further increase in the myoclonic seizures. The boy continued to suffer from febrile and nonfebrile tonic-clonic seizures.

LEV was introduced at a starting dose of 10 mg/kgbw/d and a weekly titration rate of 10 mg/kgbw up to 30 mg/kgbw/d. At the same time, VPA was tapered and stopped when the end dose of LEV was reached. At this time, the EEG demonstrated a diffuse slowing of background activity (*figure 1*). There were bilateral synchro-

nous spike-waves over the frontal regions. Short jerkings of the shoulders were associated with generalized slow-spike-and-wave-discharges. Daily seizures with twitching of the face and jerking of arms and shoulders persisted. On the 4th day of LEV-monotherapy, the boy developed myoclonic status epilepticus with continuous twitching of the face and unresponsiveness, which was controlled by intravenous midazolam after 50 minutes. Afterwards the boy was referred to our epilepsy centre for a second opinion.

The diagnosis of MAE was made according the modified ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy 1989) and was confirmed by long-term polygraphic-video-EEG/EMG recordings with frequent myoclonic seizures and myoclonic-astatic seizures (*figure 2*). MRI of the brain was normal. Neuropsychological examination revealed normal cognitive development.

LEV was discontinued and VPA reintroduced. Under VPA at 35 mg/kgbw/d, there were still frequent daily myoclonic seizures (*figure 3*). After 3 weeks of VPA-monotherapy with an unchanged seizure frequency, ethosuximide (ESM) was introduced as add-on therapy. Seizures were finally controlled with VPA (35 mg/kg bw/d) in combina-

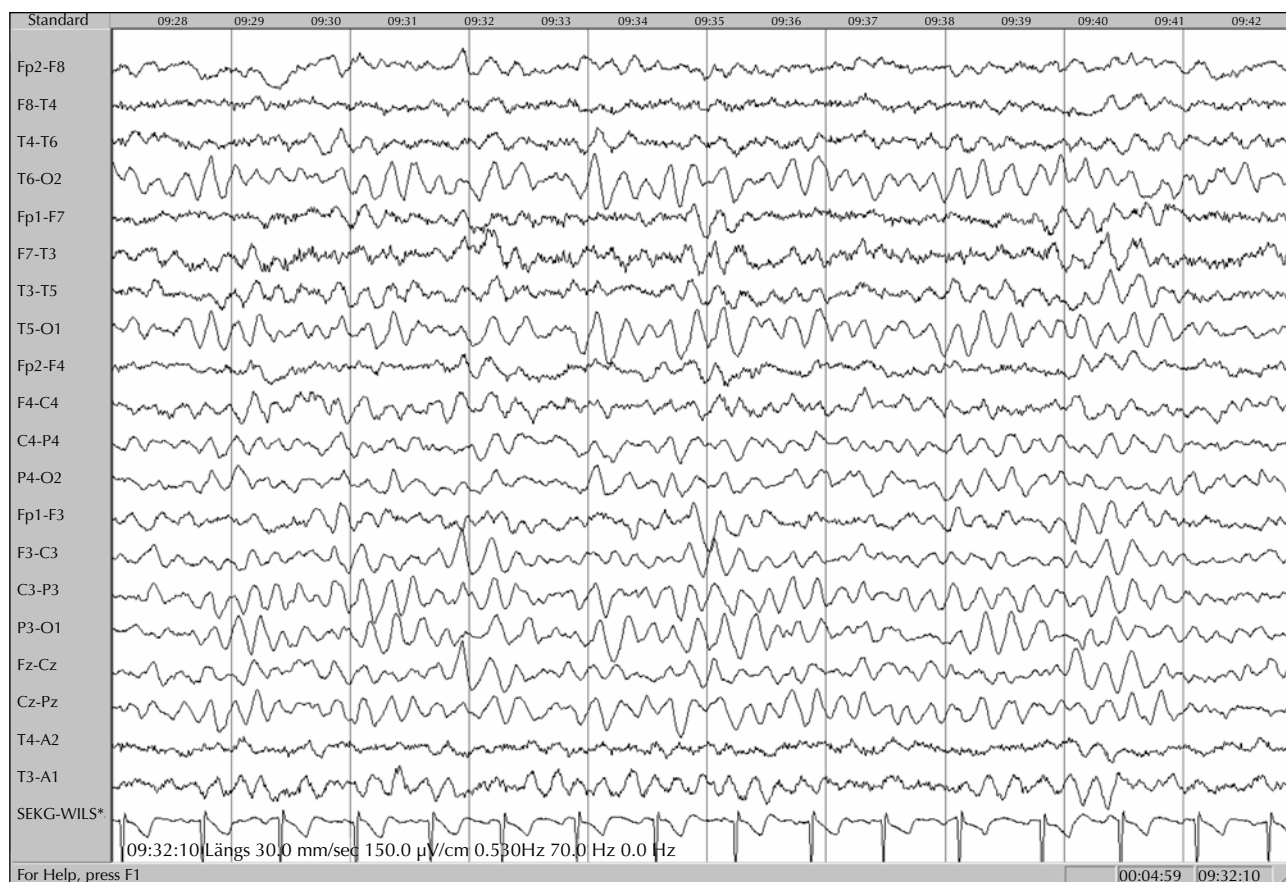


Figure 1. Awake, diffuse slowing of background activity (5/s).

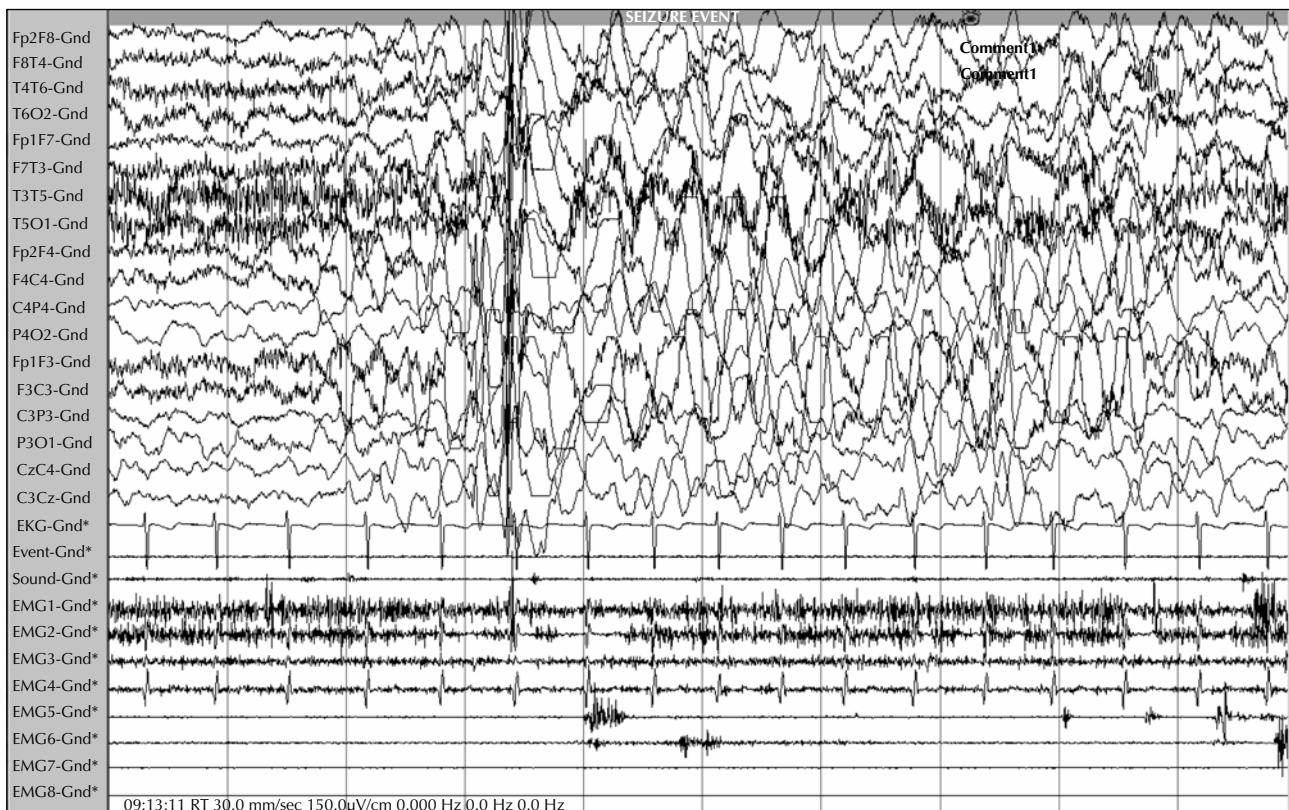


Figure 2. Polygraphic-EEG of a typical myoclonic-astatic seizure with retropulsion of the head followed by short head-nodding. Ictal EEG shows a generalized spike-wave discharge. Time locked with the generalized spike-wave-discharge EMG of the neck, trunc and the deltoids shows a burst lasting 80 ms followed by a silent period lasting around 110 ms. EMG 1 (neck), EMG 2 (trunc), EMG 3 (right deltoid), EMG 4 (left deltoid), EMG 5 (right quadriceps muscle), EMG 6 (left quadriceps muscle).

tion with ESM (14 mg/kg bw/d). The EEG showed no more epileptiform discharges and normal background activity (figure 4). Over 18 months follow-up, only one tonic-clonic seizure has occurred during an episode of fever. There have been no more myoclonic seizures or myoclonic-astatic seizures.

Discussion

The clinical observation of paradoxical drug-induced worsening of seizures is a well known phenomenon in epileptology. In general, risk factors for a seizure-inducing effect of AEDs are young age, mental retardation, antiepileptic polytherapy, high seizure frequency, and prominent epileptic activity in the EEG (Bauer 1996, Guerrini *et al.* 1998). Clinically, it can be very difficult to detect a cause-effect relationship between the introduction of a new AED and the worsening of seizures. In particular, in difficult-to-treat epilepsy syndromes an increase in seizure frequency may only reflect the natural course of the disease.

MAE is a rare, childhood epilepsy syndrome characterised by different seizure types. Myoclonic and myoclonic-astatic seizures occur in all children, tonic-clonic seizures

are the second, most frequent seizure type (Doose 1992, Guerrini *et al.* 2005). As in our case, in the majority of patients, febrile and nonfebrile tonic-clonic seizures precede the onset of the typical myoclonic and myoclonic-astatic seizures (Kaminska *et al.* 1999, Oguni *et al.* 2002). Thirty-six percent of patients develop status epilepticus, with features of atypical absences, myoclonus and astasia to varying degrees lasting hours or even a few days (Doose *et al.* 1970, Dulac *et al.* 1998). Diagnosis relies on clinical characteristics and polygraphic-video-EEG/EMG recordings; outcome is difficult to predict. Fifty to 89% of patients have a favourable outcome (Doose 1992, Kaminska *et al.* 1999, Oguni *et al.* 2002). There have been no controlled trials for the treatment of MAE. In clinical practice, VPA is the drug of choice and is the most commonly used. ESM can be effective, especially when myoclonic and absence seizures dominate the clinical presentation.

Because of its anti-myoclonic effect, LEV seems to be an interesting alternative for children with MAE suffering from resistant myoclonic-astatic seizures after failure of first-line treatment. From uncontrolled studies, there is clinical evidence that LEV possesses efficacy against myoclonic seizures in paediatric patients (Wheless and Ng 2002,

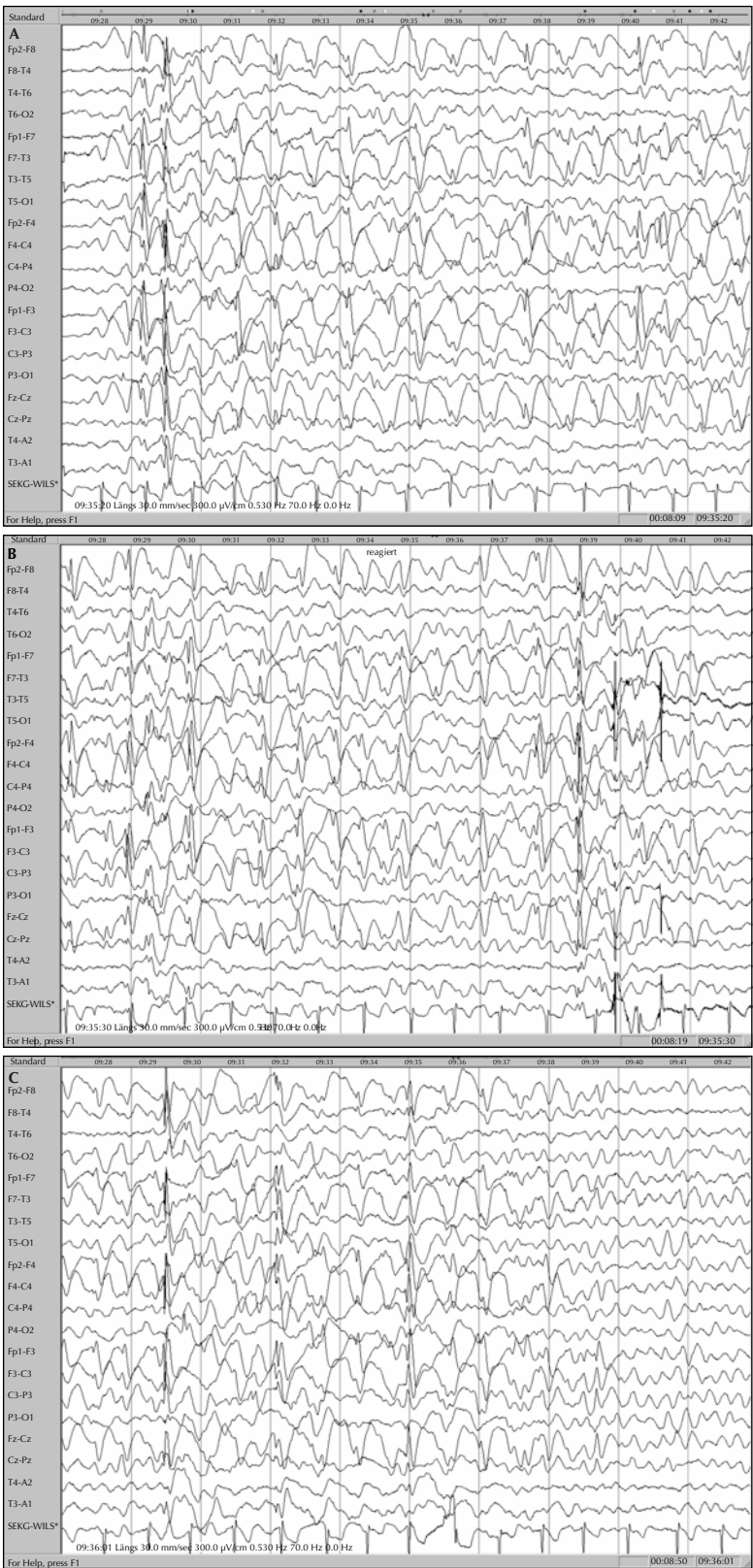


Figure 3. Prolonged runs of bilateral synchronous spike-waves associated with irregular twitching of the eyelids.

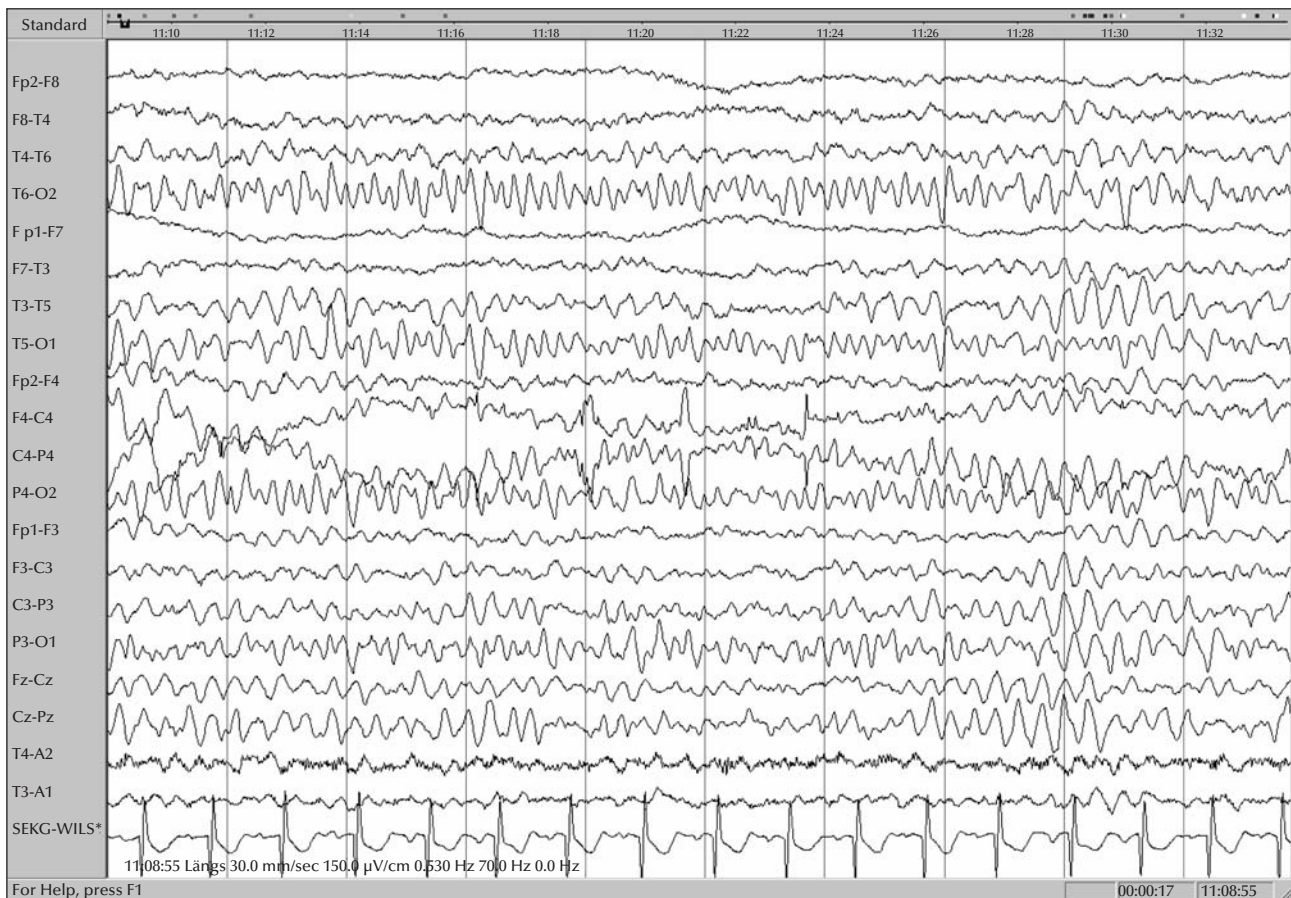


Figure 4. Child awake, normal background activity, seizure-free.

Glauser and Dulac 2003, Lagae *et al.* 2003, De los Reyes *et al.* 2004). There is only anecdotal evidence that LEV has a positive effect on MAE. Grosso *et al.* (2005) reported a reduction in seizure frequency > 50% in 4/6 patients with MAE. Other uncontrolled studies suggest a seizure inducing effect of LEV in paediatric patients, but clinical data are inconclusive. In particular, the effects of initial dose and titration rate are hotly debated. Nakken *et al.* (2003) reported, in an open prospective clinical study, exacerbation of seizure frequency in 43% (19/44) of children with intractable epilepsy, four children developed status epilepticus. Exacerbation occurred most often in mentally retarded patients during the first two months of treatment. During titration, one child developed complex partial status epilepticus, and another nonconvulsive status epilepticus. Two children developed status epilepticus after five and seven months. The authors discuss a possible seizure-inducing effect of LEV at doses above 30 mg/kgbw/d. In this context, they suggest that an increase in seizure frequency may be the only clinical sign of AED-intoxication. Coppola *et al.* (2004) showed, in a prospective, open, add-on study in a very heterogeneous group of 99 patients aged 12 months to 32 years with partial or generalised

seizures due to cryptogenic or symptomatic epilepsy, a worsening of seizures in 23.2%. This occurred during the initial treatment phase at doses less than 20 mg/kgbw/d. In addition, Tan and Appleton (2004) have shown in a retrospective case notes review of 26 children aged 10 years and younger, that in three children, pre-existing myoclonic seizures became worse after introduction of LEV given at a maximum dose of 35 mg/kgbw/d. There was no obvious association with either initial dose or rate of titration.

Our case is the first report of myoclonic status epilepticus induced by LEV in a child with MAE. It is well known that in MAE, episodes of myoclonic status can be triggered by carbamazepine and vigabatrin (Lortie *et al.* 1993, Kamin-ska *et al.* 1999, Guerrini *et al.* 2002). In our patient, myoclonic status developed after the usual titration phase under monotherapy with LEV. There were no clinical signs of drug intoxication. At the same time VPA was tapered. A causal relationship between the withdrawal of VPA and the myoclonic status is rather improbable as the myoclonic seizures were not controlled by VPA before introduction of LEV and persisted with an unchanged high daily frequency after reintroduction of VPA-monotherapy.

It can be questioned whether the myoclonic status in our patient reflected an individual adverse reaction to LEV or was the only sign of drug intoxication. However, we cannot exclude the possibility of a spontaneous aggravation of MAE, for which LEV proved inefficacious. A reintroduction of LEV would be the only way to prove these hypotheses but was not performed for ethical reasons. In summary, the anti-myoclonic effect of LEV in paediatric patients might be influenced by dosage, the patient's age or a synergistic effect of anticonvulsive co-medication. A controlled study would allow a better definition of the role of LEV in the treatment of MAE. □

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