EXPERT REVIEWS

Treatment of myoclonic seizures

Expert Rev. Neurother. 12(12), 1411–1418 (2012)

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Myoclonic seizures are sudden, brief, shock-like contractions that can vary in distribution and intensity. They may be present in different epilepsy syndromes, including some idiopathic generalized epilepsy, epileptic encephalopathies and progressive myoclonus epilepsies. Despite the fact that there are many studies about the pathophysiology of myoclonic seizures and clear descriptions of the different myoclonic epilepsy syndromes, relatively little has been written on treatment. Valproate and some benzodiazepines are widely used to treat myoclonic seizures. In addition, more treatment options exist today as there is emerging evidence to support the efficacy of some newer antiepileptic drugs. On the other hand, some myoclonic epilepsies remain refractory to drug treatment and some antiepileptic drugs may exacerbate or even induce myoclonus. In the coming years, better understanding of mechanisms of myoclonic seizures and myoclonic epilepsies could result in great improvement of therapy and the quality of life of patients.

Keywords: antiepileptic drugs • clinical trials • epilepsy • myoclonic seizures • myoclonus • review • treatment

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Release date: 7 December 2012; **Expiration date:** 7 December 2013

Learning objectives

Upon completion of this activity, participants will be able to:

- Describe the role of valproate and some benzodiazepines to treat myoclonic seizures, based on a review
- Describe the role of other antiepileptic drugs in treatment of myoclonic seizures
- Describe nonpharmacological management of myoclonic seizures, based on a review

 10.1586/ERN.12.90 ISSN 1473-7175

Financial & competing interests disclosure
Editor
Elisa Manzotti
Publisher, Future Science Group, London, UK.
Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.
CME Author
Laurie Barclay
Freelance writer and reviewer, Medscape, LLC
Disclosure: Laurie Barclay, MD, has disclosed no relevant financial relationships.
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Myoclonus refers to sudden, brief (<350 ms), shock-like involuntary movements, caused by muscular contraction (or inhibition in the case of negative myoclonus) anatomically arising from the cortex, subcortex or spinal cord. Myoclonus can be observed in patients with various clinical conditions including response to infection, head or spinal-cord injury, stroke, brain tumors, kidney or liver failure, lipid storage disease, chemical- or drug-poisoning [1,2]. Myoclonic seizures may vary in their distribution and intensity of manifestations and they can be generalized or confined to individual muscles or groups of muscles. They may be present in different epilepsy syndromes, including some idiopathic generalized epilepsies (IGEs; e.g., benign myoclonic epilepsy of infancy or juvenile myoclonic epilepsy [JME]), some epileptic encephalopathies (e.g., Dravet syndrome [DS]), or the group of progressive myoclonus epilepsies [1,2], with significant semiologic and EEG differences, as well as similarities [3]. In addition, non-epileptic myoclonus often produce apparently similar clinical pictures indistinguishable from myoclonic seizures and a wrong diagnosis may lead to incorrect treatment choices that can indeed worsen a patient's condition [2,3]. Epilepsy syndromes that usually include myoclonic seizures begin mostly in childhood, although this seizure type can occur at any age. A list of epileptic conditions in which myoclonic seizures occur is shown in **Box 1**.

Box 1. Epileptic conditions in which myoclonus seizure may occur.

- Early myoclonic epilepsy in infancy
- Severe myoclonic epilepsy of infancy (Dravet syndrome)
- Juvenile myoclonic epilepsy (Janz syndrome) and idiopathic generalized epilepsies with variable phenotypes
- Eyelid myoclonia with absences (Jeavons syndrome)
- Familial infantile myoclonic epilepsy
- Familial cortical tremor, myoclonus and epilepsy
- Reflex epilepsies, including occipital photosensitive epilepsies and primary reading epilepsy
- Epilepsy with myoclonic absences
- Epilepsy with myoclonic-astatic seizures (Doose syndrome)
- Lennox–Gastaut syndrome
- Myoclonic status in fixed encephalopathies
- Epilepsia partialis continua (focal myoclonus)
- Progressive myoclonic epilepsies
- Other symptomatic epilepsies (e.g., Angelman syndrome, Alzheimer's disease, celiac disease)

Modified with permission from [2].

Treatment of myoclonic seizures

Despite the large amount of studies about pathophysiology of myoclonic seizures and clear descriptions of the different myoclonic epilepsy syndromes, relatively little has been written on treatment, which is mainly based on clinical experience and prospective and retrospective studies [4].

Valproate (VPA) is often a good choice to treat myoclonic seizures in men whereas lamotrigine (LTG) is usually preferred in women owing to the teratogenicity and side effects of VPA. Levetiracetam (LEV) and topiramate (TPM) are also highly effective and are often used in combination or as second-line treatment. Some antiepileptic drugs (AEDs) can aggravate myoclonic seizures. Here it follows an overview of the available therapeutic options for the treatment of myoclonic seizures in the context of different epileptic syndromes.

Benzodiazepines

Clonazepam (CZP) was introduced for the treatment of epilepsy when rigorous, randomized, double-blind trials were not always required for drug registration. However, there is no doubt that CZP has significant efficacy for most seizure types and, in particularly, it is effective for myoclonic seizures [5–7]. In a single-blind comparative study of clobazam with CZP in Lennox–Gastaut syndrome, the first showed better global improvement against all seizure types excepting for myoclonic seizures [8]. Nevertheless, CZP is used infrequently as an initial therapy because there are alternatives with fewer adverse effects.

There are only few publications about nitrazepam but the drug has been described as effective for myoclonic seizures in children [9].

Lamotrigine

LTG has been introduced as adjunctive treatment and monotherapy of partial seizures (with or without secondary generalization) and primary generalized tonic-clonic seizures (PGTCS) [10]. Several open-label studies suggest that LTG is efficacious against all seizure types in patients with JME [11,12]. In a retrospective study that included 72 patients with JME, no significant differences in seizure control were found between VPA and LTG in either monotherapy or polytherapy [13]. However, in the SANAD study, VPA was found to be significantly better than LTG in patients with different forms of epilepsy [14]. Because of the minor impact on weight gain and the significantly lower risk of major malformations in exposed infants, LTG monotherapy should be considered first in women of childbearing age [15]. However, since some studies reported myoclonic seizure exacerbation by LTG in 5–14% of patients with JME [13,16], doubts have been raised about the rationale for using LTG in this particular form of epilepsy. Moreover, LTG can aggravate myoclonus either in benign forms of epilepsy [17] than in progressive myoclonic epilepsies [18] and aggravation of severe myoclonic epilepsy in infancy or DS is particularly common with LTG [19,20]. Finally, myoclonus can represent a new symptom when LTG is initiated in patients with genetically determined forms of epilepsy [21].

Levetiracetam

Levetiracetam is a broad-spectrum AED sharing common chemical structures with other pyrrolidone derivatives, such as piracetam and brivaracetam, and binding to synaptic vesicle protein SV2A, the drug is indicated in adults as a monotherapy in the treatment of partial-onset seizures and as adjunctive treatment of myoclonic seizures and generalized tonic–clonic seizures. In a recent double-blind, placebo-controlled trial, LEV (3000 mg/day) was shown to be highly effective as adjunctive therapy in 120 IGE patients aged 12–65 years with uncontrolled myoclonic seizures, with 58.3% of patients achieving >50% reduction in myoclonic seizure days per week, compared with 23.3% in the placebo group ($p < 0.001$) [22]. In this study, the myoclonic seizure-reducing effect of LEV occurred within the first 2 weeks of treatment at a LEV starting dose of 1000 mg/day, and was sustained during the entire treatment period.

Another double-blind, placebo-controlled trial has shown adjunctive LEV to be effective in controlling generalized tonic-clonic seizures, myoclonic seizures and all seizures type in patients with IGE compared with placebo. The median percentage reduction in seizure days per week between the prospective baseline period and treatment period was 62.8% for LEV and 24.7% for placebo ($p < 0.001$) [23].

The results of these two double-blind, placebo-controlled studies are in line with the findings of open-label studies, confirming the usefulness of LEV in IGEs with myoclonic seizures [24–27]. Although placebo-controlled trials are few, more than 60% of patients with intractable JME, one of the most common forms of IGE, became seizure-free with LEV monotherapy or polytherapy [24]. Notably, and uniquely among new AEDs, LEV efficacy has been established in clinical photosensitivity [27–29]. Moreover, LEV reduces or eliminates both the photoparoxysmal responses and the myoclonic jerks elicited by intermittent photic stimulation [27,30]. LEV has also demonstrated to be an excellent choice in patients with Jeavons syndrome to treat eyelid myoclonia with or without absences and photosensitivity [31]. Finally, open-label, add-on trials have assessed the efficacy of LEV even in traditionally, refractory epileptic conditions, such as severe myoclonic epilepsy of infancy or DS [32], Rett syndromes [33], and different forms of progressive myoclonic epilepsies [34]. However, placebo-controlled studies are needed to establish LEV long-term efficacy and whether this drug may be considered as a first choice treatment for these severe conditions, also considering the common precipitation of behavioral disturbances due to this drug.

Valproate

VPA has been in clinical use for the treatment of epilepsy for more than 40 years and, until the 1990s, it has been the only drug with a very broad spectrum of activity against different seizure types, both generalized and focal. VPA was first proposed as a treatment of myoclonic seizures about 28 years ago [35]. Few randomized double-blind studies have been performed using VPA in IGEs, of these; one study has evaluated VPA in JME comparing low-dose (1000 mg/day) and high-dose (2000 mg/day) VPA monotherapy [36]. Seizure control did not differ between doses: 37 versus 44% were seizure-free during low-dose and high dose VPA treatment, respectively; 25% were seizure-free for the entire study [36].

A number of studies showed a 41–88% seizure-free rate for patients receiving VPA, either as an add-on medication or as monotherapy in JME [37,38]. In particular, VPA monotherapy was assessed in 22 patients with myoclonic seizures and, in 18 out of these 22 patients, myoclonic seizures were controlled by VPA monotherapy [39]. In another study, 16 out of 23 patients with myoclonic epilepsy of adolescence experienced full seizure control with VPA monotherapy [40]. VPA is currently a first-line drug in all forms of IGEs and it remains a drug of first choice in the treatment of pediatric epilepsies [41].

Topiramate

TPM is a newer broad-spectrum agent licensed as adjunctive therapy against partial and secondarily generalized seizures [42]. TPM is also useful for PGTCS [43] and Lennox–Gastaut syndrome [44]. Although double-blind, randomized, controlled trials have demonstrated that TPM is effective in PGTCS [43,45], similar Class I evidence is not available for TPM in myoclonic seizures. Two retrospective cohort studies [13,46] investigated whether TPM monotherapy or polytherapy was an effective option in the treatment of all seizure types in patients with IGEs. Although TPM treatment appears to be a useful option with encouraging results, more data are needed to determine whether it is an effective option as monotherapy in patients with IGE. Finally, the numbers of patients in these studies were too small to draw a conclusion about the effect of TPM on myoclonus.

Zonisamide

Zonisamide (ZNS) is a new AED, with multiple mechanisms of action that has been available in South Korea and Japan since 1989, and it has been extensively used in children, with good efficacy and tolerability, to treat partial and generalized onset seizures [47]. In an open-label, retrospective study, ZNS was shown to be an effective and well-tolerated drug in the treatment of patients with JME [48]. In this study, overall 80% of patients on ZNS monotherapy showed good control (≥50% seizure reduction) and 62% of patients were free of myoclonic seizures. Recently, the effect of ZNS has been suggested also against myoclonic seizures in patients with progressive myoclonic epilepsy in two open-label studies [49,50].

Antiepileptic drugs aggravating myoclonic seizures

Of major importance remains avoidance of medication that may aggravate myoclonic seizures (Table 1): carbamazepine (CBZ), phenytoin, vigabatrin, and, to a lesser extent, LTG [51,52]. Notably, the use of VPA is not advised in children with an undiagnosed metabolic condition or mitochondrial disorders because of the increased risk of hepatotoxicity and encephalopathy [53]. The worsening effect of LTG has been mostly reported in patients with DS [19,20]. Myoclonic seizures may be precipitated by treatment with LTG [17] and CBZ in children with rolandic epilepsy with neurophysiological evidence of epileptic negative myoclonus [54]. The latter is a well-known side effect of some anticonvulsant drugs such as CBZ, VPA, phenytoin, LTG, pregabalin [55] and oxcarbazepine [54] and lacosamide [56]. In this sense, an inverse pharmacodynamic effect has been claimed as the main mechanism of aggravation of myoclonias in IGEs [52]. It is worth noting that myoclonus in symptomatic generalised epilepsies (as in progressive myoclonus epilepsy or in Angelman syndrome) are generally aggravated by the same drugs that aggravated IGEs [52,57].

Nonpharmacological treatments

It is well known that in several myoclonic epilepsy syndromes, such as JME and other forms of IGEs, sleep deprivation and alcohol intake can induce seizures and the sleep–wake rhythm has to be regulated. Accordingly, all circumstances interfering with normal sleep should be avoided. The use of alcoholics should be minimized or permitted only in rare occasions. In case of photosensitivity, patients should avoid significant visual stimuli or use specific eyeglasses and increased distance from a video-display [58].

Dietary therapy is gaining increasing attention in patients with epilepsy. Recently, a proof-of-concept trial of the whey protein α-lactalbumin failed to be proven effective in patients with different syndromes featuring chronic cortical myoclonus [59]. The ketogenic diet has been used successfully in a variety of epilepsy syndromes with multiple etiologies, including DS, Lennox–Gastaut syndrome and myoclonic-astatic epilepsy [60,61]. It is still unclear whether ketogenic diet is more effective in certain epilepsy syndromes. Nevertheless, although the diet's utility in epilepsy syndromes of various etiologies and in some neurodegenerative disorders suggests it may have multiple mechanisms of action, it is quite well clear that the diet should be considered early in the course of treatment [60,61].

An additional issue that merits further attention in the upcoming years is the potential efficacy of vagus nerve stimulation therapy. This therapeutic option has been successfully considered in case of severe, refractory progressive myoclonic epilepsy, resulting in improved quality of life and good ability to perform activities of daily living [62]. Moreover, the effects of vagus nerve stimulation on seizure control and cerebellar dysfunction may provide clues to the underlying mechanism of action.

Table 1. Overview of the treatment of myoclonic epilepsies.

	Diagnosis	Dose	Adverse events	Worsening	Ref.
Clonazepam	Lennox–Gastaut DS; myoclonic seizures in IGEs	3–6 mg/day	Agitation, confusion, aggressiveness	Paradoxical hyperactivity (particularly in children)	[5,6]
Valproate	BMEI; JME; MA; MAE; DS	20–30 mg/kg/day	Weight gain, rare teratogenicity, severe liver toxicity (particularly in children)	Rare	[35,39,41]
Lamotrigine	JME; MAE	200–400 mg/day Children 2–12 years: 2.5–7.5 mg/kg/day	Skin rush, dizziness, diplopia	DS; JME	[19,21]
Levetiracetam	DS; PME; EMA; JME; myoclonic seizures in IGE	1000–3000 mg/day	Somnolence, behavioral and psychiatric disturbance, seizure aggravation in IGE	Absence seizures	[22,27,31,34,60]
Topiramate	JME	100–500 mg/day (adults) 2–9 mg/kg/day (children)	Dizziness, weight loss, cognitive dysfunction	Rare	[13,46]
Zonisamide	DS; PME; JME	200–600 mg/day (adults) 489 mg/kg/day (children)	Dizziness, memory impairment, somnolence	Rare	[47–50]

BMEI: Benign myoclonic epilepsy in infancy; DS: Dravet syndrome; EMA: Eyelid myoclonia and absence; IGE: Idiopathic generalized epilepsy; JME: Juvenile myoclonic epilepsy; MA: Myoclonic absence; MAE: Myoclonic astatic epilepsy; PME: Progressive myoclonic epilepsy.

Expert commentary

In theory, any etiological factor leading to brain damage can be associated with myoclonic seizures. Thus, myoclonus may be present in a variety of CNS disorders, such as Alzheimer's disease, subacute sclerosing panencephalitis, Creutzfeldt–Jakob disease, and many forms of severe epilepsy [2]. The correct identification of the associated neurological condition in which myoclonus seizures occur is crucial for appropriate treatment. Clinical and EEG features are in particular extremely useful to determine the features of myoclonic epilepsy. In addition, a detailed electrophysiological study is often mandatory to obtain a definite diagnosis [3].

Despite the availability of numerous treatment options, the treatment of myoclonic seizures continues to be challenging. Notably, there have only been two treatments (CZP and LEV) licensed specifically for myoclonic seizures and evidence-based data to guide selection of AED therapy for patients who have IGE with myoclonic seizures are limited. Myoclonus is often not the only seizure type within an epilepsy syndrome and only some antiepileptic drugs are antimyoclonic. In addition, some myoclonic epilepsies still remain refractory to drug treatment and some antiepileptic drugs may exacerbate or even induce myoclonus.

In the treatment of myoclonic seizures, experience with VPA is of longer duration and involves greater numbers of patients that with new AEDs. Although very few randomized controlled trials have been performed regardless of the treatment of myoclonic seizures, VPA is considered the drug of choice particularly when myoclonic seizures are considered to be components of 'benign' epilepsies. Newer AEDs such as LTG, LEV, TPM and ZNS represent treatment options in patients with IGEs and refractory myoclonic seizures [63]. There are no class I comparative studies to show whether these newer drugs are as effective as VPA in the IGEs, however, because of overall better tolerability, they have been proposed as alternative first-line agents in women with childbearing potential [63]. Even if broad-spectrum AEDs are not effective against all generalized seizures, they are less likely to aggravate myoclonic seizures [51]. JME is one of the most common IGEs that usually requires lifelong treatment, and at least half of the patients are women of childbearing age who may be exposed to the teratogenic effects of VPA. Moreover, comorbidities such as migraine, obesity and mood disorders may also impact the choice of AED therapy in patients with JME and it could be reasonable to recommend one of the new AEDs as initial treatment of such patients [64]. LEV can be firstly considered when myoclonic seizures are the dominant seizure type, whereas there is still insufficient evidence for the use of TPM or ZNS as monotherapy. Myoclonus aggravation by some AEDs should be carefully kept in mind to avoid seizure worsening and incorrect diagnosis of epilepsy syndrome. Finally, special attention should be paid to extremely drug-resistant conditions, such as Rasmussen encephalitis, an inflammatory unihemispheric brain disorder featuring repetitive focal myoclonus (i.e., epilepsia partialis continua) for which no significant treatment options are available except for functional hemispherectomy at the price of irreversible loss of functions located in the affected hemisphere [65].

Five-year view

Treatment of myoclonic seizures and myoclonic epilepsies has been poorly addressed so far by the recent literature. However, there is emerging evidence to support the efficacy of some newer AEDs. Great attention is now required to recruit and maintain patients into drug trials as well as to aid the understanding of adverse events and drug interactions. We also need a better understanding of the long-term adverse effects of AEDs. In addition, more data are needed over the next 5 years to determine whether targeting new molecular mechanisms represents a feasible strategy to pursue for clinical applications. In this sense, most of this work will need to continue to be pursued on the basic research level, primarily in animal models. Finally, even if newer drugs will appear to be efficacious, more detailed studies in animals should be performed to determine optimal methods of drug delivery and potential toxicities of the drugs. In fact, only better understanding of mechanisms of myoclonic seizures and myoclonic epilepsies could result in great improvement of therapy and quality of life of patients.

Key issues

- Myoclonic seizures can be associated to several epilepsy syndromes, including some forms of idiopathic generalized epilepsy, epileptic encephalopathies or progressive myoclonus epilepsies.
- Treatment of myoclonic seizures is mainly based on prospective and retrospective studies, with little evidence from randomized clinical trials.
- Traditionally, valproate is the first choice to treat myoclonic seizures in men. In women, lamotrigine is usually preferred, owing teratogenicity and side effects of valproate. In addition, levetiracetam, zonisamide and topiramate are effective and can be used in combination or as second-line treatment.
- Because myoclonic seizures can be difficult to treat, clinicians should be flexible in their approach and tailor therapy to each patient.
- Of major importance remains avoidance of medication that may aggravate myoclonic seizures. In particular, induction of myoclonic seizures may be seen with the use of lamotrigine and carbamazepine.
- It is well known that in most forms of myoclonic epilepsy, lack of sleep and alcohol intake can induce seizures. Patients should be advised that some nonpharmacological strategies allow optimal seizure control even without concomitant drug therapy, especially in idiopathic generalized epilepsies.
- Better understanding of pathophysiologic mechanisms of myoclonic seizures and myoclonic epilepsies could yield great improvement in the treatment and quality of life of patients.

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•• of considerable interest

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Your patient is a 3-year-old girl with myoclonic seizures. Based on the review by Drs. Striano and Belcastro, which of the following statements about the role of valproate (VPA) and/or benzodiazepines in her treatment is most likely correct?

- ☐ **A** Seizure-free rate for patients receiving VPA as monotherapy or as an add-on medication in juvenile myoclonic epilepsy (JME) is 41%–88%, based on several studies
- ☐ **B** Seizure-free rate for patients receiving VPA in JME is significantly lower with high-dose VPA than with low-dose VPA
- ☐ **C** Clonazepam is widely used as initial therapy
- ☐ **D** Nitrazepam has been shown to be ineffective for myoclonic seizures in children

2. Based on the review by Drs. Striano and Belcastro, which of the following statements about the role of other antiepileptic drugs (AEDs) in treatment of myoclonic seizures is most likely correct?

- ☐ **A** In women, valproate is usually preferred over lamotrigine
- ☐ **B** Levetiracetam, zonisamide, and topiramate are effective for treatment of myoclonic seizures
- ☐ **C** Levetiracetam has no behavioral adverse effects
- ☐ **D** Double-blind, randomized, controlled trials have proven that topiramate is highly effective for treatment of myoclonic seizures

3. Based on the review by Drs. Striano and Belcastro, which of the following statements about nonpharmacological management of myoclonic seizures for the patient described in question 1 would most likely be correct?

- ☐ **A** Sleep hygiene and regulation of alcohol intake play no role in management of myoclonic seizures
- ☐ **B** The whey protein alfa-lactalbumin has been proven effective in patients with chronic cortical myoclonus syndromes
- ☐ **C** Medication that may aggravate myoclonic seizures should be avoided, including lamotrigine and carbamazepine in some patients
- ☐ **D** There is no evidence supporting vagus nerve stimulation therapy for patients with severe, refractory, progressive myoclonic epilepsy