Review article

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Myoclonus and seizures in progressive myoclonus epilepsies: pharmacology and therapeutic trials

Roberto Michelucci [1], Elena Pasini [1], Patrizia Riguzzi [1], Eva Andermann [2], Reetta Kälviäinen [3], Pierre Genton [4]

[1] IRCCS, Institute of Neurological Sciences of Bologna, Unit of Neurology, Bellaria Hospital, Bologna, Italy
[2] Montreal Neurological Hospital & Institute, Neurology & Neurosurgery and Human Genetics, McGill University, Montreal, Canada
[3] Kuopio Epilepsy Center, Department of Neurology, Kuopio University Hospital, Finland
[4] Centre Saint-Paul - Hôpital Henri-Gastaut, Marseille, France

ABSTRACT – Generalized motor seizures, usually tonic-clonic, tonic-vibratory, myoclonic or clonic, and stimulus-sensitive/action myoclonus are typical features of progressive myoclonus epilepsies (PMEs). Despite the introduction of many anticonvulsants, the treatment of these symptoms, particularly myoclonus, remains challenging, due to the incomplete and often transitory effects of most drugs. Moreover, treatment is only symptomatic, since therapy targeting the underlying aetiology for these genetic conditions is in its infancy. Traditional antiepileptic drugs for the treatment of PMEs are valproate, clonazepam, and phenobarbital (or primidone). These drugs may improve the overall performance of PME patients by decreasing their generalized seizures and, to a lesser extent, their myoclonic jerks. Newer drugs which have been shown to be effective include piracetam, levetiracetam, topiramate, zonisamide, and possibly perampanel for Lafora disease. The potential of other drugs (such as L-triptophan and N-acetylcysteine) and procedures (such as vagal and deep brain stimulation) has also been discussed. The available data on the efficacy of drugs are mainly based on small series or anecdotal reports. Two prospective, randomized, double blind studies investigating the novel SV2A ligand, brivaracetam, in genetically confirmed Unverricht-Lundborg patients have been performed with disappointing results. When treating PMEs, particular care should be paid to avoid drugs known to aggravate myoclonus or myoclonic seizures, such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, tiagabine, gabapentin, and pregabalin. The emergency treatment of motor status, which often complicates the course of PMEs, consists of intravenous administration of benzodiazepines, valproate, or levetiracetam.

Key words: progressive myoclonus epilepsies, myoclonus, valproate, brivaracetam, perampanel, drugs worsening myoclonus

Correspondence:
Roberto Michelucci
IRCCS, Institute of Neurological Sciences of Bologna, Unit of Neurology,
Bellaria Hospital, via Altura 3,
40139 Bologna, Italy
<roberto.michelucci@ausl.bo.it>

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Progressive myoclonus epilepsies (PMEs) (Minassian *et al.*, 2016) are a group of uncommon diseases characterized by the association between myoclonus, epileptic seizures, and neurological deterioration, particularly ataxia and dementia (Marseille Consensus Group, 1990). A large number of rare specific genetic disorders may cause PME, but 5 principal causes are responsible for most cases of PME worldwide: Unverricht-Lundborg disease (ULD), Lafora disease (LD), mitochondrial encephalomyopathies (ME) with the phenotype of myoclonic epilepsy with ragged red fibres (MERRF), and sialidosis and neuronal ceroid lipofuscinoses (NCL). In order to establish a precise diagnosis, the clinical and neurophysiological characteristics of each PME are crucial to guide the clinician to the correct diagnostic algorithm, which may include complex and sometimes invasive procedures (Berkovic *et al.*, 1986; Shahwan *et al.*, 2005). Despite extensive investigations, a number of PMEs remain undiagnosed (Franceschetti *et al.*, 2014); however, these unsolved cases are decreasing over time as a result of recent genetic advances (including wide-genome/exome sequencing), which have led to the discovery of new major causative genes, such as *SCARB2* (Dibbens *et al.*, 2009) and *KCNC1* (Muona *et al.*, 2015).

Myoclonus, the main symptom of PMEs, is typically fragmentary and multifocal, involving the musculature of the face and distal limbs. Bilateral massive myoclonic jerks, which tend to involve proximal limb muscles, may also occur, sometimes causing the patient to fall to the ground. Myoclonus may be spontaneous or, more often, induced or exacerbated by a variety of stimuli (such as light, sound, touch, and emotional strain), as well as movement or posture. Action myoclonus, in which muscular jerking is induced by movement or attempts at movement, is the most frequent and disabling form, commonly seen in almost all conditions underlying PME. A mixture of positive and negative myoclonus is the rule in patients with PME, especially LD. The generators for myoclonus in PME remain controversial, but neurophysiological studies suggest that cortical reflex myoclonus is the most common type, while reticular reflex myoclonus is less frequent (Tassinari *et al.*, 1998b). Myoclonus is often difficult to control in these conditions and is usually a significant cause of disability in daily life.

PMEs are characterized by a wide range of epileptic seizures (Michelucci *et al.*, 2002). Generalized tonic-clonic seizures are usually reported at the onset of LD and ULD and may, therefore, suggest the alternative diagnosis of idiopathic generalized epilepsies. They may occur without any warning or after a long build-up of myoclonias. Polygraphic recording may reveal these generalized motor seizures to be tonic-vibratory seizures (as in LD) or true myoclonic or clonic seizures (as in ULD). Absences or focal seizures (such as occipital seizures in LD) have also been encountered.

Other symptoms, which appear at various times during the course of the illness, include ataxia, cognitive dysfunction (sometimes leading to dementia), pyramidal signs, and a variety of other neurological and extraneurological signs (particularly in mitochondrial diseases).

Overall, the treatment of PMEs remains palliative, since there is no specific treatment for most genetic disorders underlying a PME syndrome (Uthman & Reichl, 2002; Shahawan *et al.*, 2005). Despite a variety of anticonvulsants on the market, effective treatment remains challenging due to the fact that although these drugs may control major convulsive seizures, myoclonus does not really respond to the use of classic antiepileptic drugs (AEDs). Moreover a pathogenetic variety exists among the subtypes of PME, which means that medications which benefit one patient may be less effective in patients with another particular type of PME. Another problem is that clinical trials are difficult to perform due to the small number of patients, the progression of the clinical condition, and the choice of reliable efficacy endpoints. Hence, available data on the efficacy of newer antiepileptic medications in PME are primarily anecdotal or observational, based on individual responses in very small groups of patients.

In the present review, we summarize the results of the treatment of PMEs using a number of drugs (including AEDs) and procedures. The issues of designing and performing controlled clinical trials, as well as the emergency treatment, for patients with PMEs are also addressed.

Pharmacological treatment

Traditional AEDs used to treat PMEs are valproate, clonazepam, and phenobarbital (or primidone, a parent compound). These drugs may improve the overall performance of PME patients by decreasing their generalized seizures and, to a lesser extent, their myoclonic jerks. Other drugs which have shown to be effective include piracetam, levetiracetam, topiramate, zonisamide, brivaracetam, and perampanel (at least for LD). The overall therapy of PMEs is summarized in *table 1*.

Valproate

Valproate (at doses ranging from 15 mg/kg to 60 mg/kg) is the treatment of choice for PMEs. It may be used as monotherapy in mild cases or combined with other drugs in more serious cases. Its usefulness was clearly demonstrated by Iivanainen & Himberg (1982) in a prospective study conducted with 26 Finnish adults

Table 1. Treatment of PMEs. (A combination of multiple drugs is commonly needed).

First-line AEDs	Second-line AEDs	Third-line strategies	Emergency treatment
Valproate	Zonisamide	5-hydroxy-L-tryptophan	Benzodiazepines i.v.[1]
Clonazepam	Levetiracetam	Lamotrigine	Levetiracetam i.v.
	Topiramate	N-acetylcystein	Valproate i.v.
	Piracetam	VNS or DBS	Phenytoin i.v.[2]
	Phenobarbital	Experimental drugs	
		Brivaracetam	
		Perampanel[3]	

[1] Diazepam, lorazepam, clonazepam, midazolam.
[2] Phenytoin may be succesfully used to treat motor status epilepticus in late-stage PMEs (Miyahara *et al*., 2009).
[3] Used thus far for Lafora disease.

with severe forms of PME, likely to be related to ULD. These patients were severely disabled at the onset of the study (due to stimulus-sensitive myoclonus and ataxia) and were receiving chronic treatment with different combinations of AEDs, including carbamazepine, phenytoin, phenobarbital, primidone, and diazepam. These drugs were discontinued and treatment with valproate and clonazepam was commenced simultaneously, with rapid titration to optimal doses (1,500 to 1,800 mg for valproate and 6 to 10 mg for clonazepam). If the patients still had generalized tonic-clonic seizures, 50 to 100 mg of phenobarbital was added. The patients showed a dramatic improvement, particularly in locomotor ability, which continued in the 19 patients who were followed for 6 years. According to Iivanainen & Himberg (1982), these favourable results contributed to improving the prognosis of 'Baltic' PME and were also due, at least in part, to the discontinuation of phenytoin.

Despite its widespread use for all types of PME, valproate should be given with caution for mitochondrial disorders, due to its inhibitory effect on complex IV (cytocrome c oxidase) activity in the respiratory chain (Lam *et al*., 1997) and carnitine uptake (Tein *et al*., 1993). If used, therefore, supplementation with L-carnitine is recommended (Tein *et al*., 1993).

Clonazepam

The efficacy of clonazepam for the treatment of myoclonus and myoclonic seizures in different clinical contexts is well established (Nanda *et al*., 1977; Obeid & Panayiotopoulos, 1989; Tassinari *et al*., 1998a). The role of clonazepam in PMEs was highlighted in the study of Iivanainen & Himberg (1982), as described in the above section. Clonazepam is used as add-on therapy, at doses ranging from 3 to 16 mg/day for adults and 0.2 mg/kg/day for children. Due to the possible development of tolerance in some patients after one to 6 months of treatment, the dosage may need to be adjusted. Since it is commonly used in combination with other drugs for PMEs, the sedative effects of clonazepam may increase with the concomitant administration of phenobarbital. The effect of other, commonly used benzodiazepines, such as diazepam or clobazam, has not been assessed. However, these drugs may be used alternatively, especially when tolerance to clonazepam has developed.

Phenobarbital

Phenobarbital is a major AED with a wide efficacy spectrum. In PMEs, it may be used as an add-on treatment, at doses ranging from 30 to 200 mg/day (adults) and 3 to 8 mg/kg/day (children), particularly for the control of generalized tonic-clonic seizures (Iivanainen & Himberg, 1982). Particular attention should be paid to the inhibitory effect of valproate on phenobarbital elimination, resulting in phenobarbital accumulation and increased somnolence. Toxic signs may also be precipitated by elevated blood ammonia levels, because the magnitude of valproic acid-induced hyperammonaemia is increased in patients comedicated with phenobarbital (Michelucci *et al*., 2009). Primidone, which is at least partially metabolized into phenobarbital, has also been used with positive results in patients with myoclonus (Obeso, 1995).

Piracetam

Piracetam, a pyrrolidone derivative with a potent antimyoclonic effect and good tolerability profile, has long been used for the treatment of PMEs. Koskiniemi *et al*. (1998) reported a significant

reduction in myoclonic jerks, and improvement in gait, in a double-blind, placebo-controlled trial in 20 patients with ULD, especially with the highest dose used (24 g/day). In this study, a linear dose-effect relationship of piracetam was established. High piracetam doses (up to 45 g/day) were also used by Genton *et al.* (1999) to obtain a stable and long-lasting improvement in 12 patients with PME.

Other reports have also stressed the positive antimyoclonic effects of 20 g/day for advanced forms of PMEs (Fedi *et al.*, 2001). The major drawback of these higher doses is the number of tablets taken and their bulk, sometimes making adherence to treatment difficult. Piracetam is well tolerated and the side effects (usually consisting of gastrointestinal discomfort) are rare, transitory, and mild even at high doses and can be avoided by slow titration (Ikeda *et al.*, 1996).

Levetiracetam

Levetiracetam, a potent AED with a wide spectrum and a unique mechanism of action (mediated by binding to presynaptic vescicular protein, SV2A), was developed within the class of pyrrolidone derivatives and belongs to the same family of piracetam. For PMEs, levetiracetam has been evaluated in several series and appears to be effective for both myoclonus and generalized seizures (Genton & Gelisse, 2000; Frucht *et al.*, 2001; Kinrions *et al.*, 2003; Crest *et al.*, 2004; Magaudda *et al.*, 2004; Lim & Ahmed, 2005; Mancuso *et al.*, 2006; Papacostas *et al.*, 2007).

Overall, of 23 patients with ULD treated with levetiracetam in open label trials at doses ranging from 1,000 to 4,000 mg, 15 (65 per cent) showed some clinical improvement while 8 (35 per cent) were unchanged. Seven patients (30 per cent) showed a dramatic improvement, which tended to subside, however, with long-term treatment. Levetiracetam is usually well tolerated in this group of patients and does not interact with concomitant drugs used for PMEs.

Topiramate

Topiramate, a sulfamate-substituted monosaccharide molecule, is a widely recognized broad-spectrum AED which is particularly effective for the treatment of refractory focal seizures, as well as primary or secondary generalized seizures. There are scattered reports in the literature showing that topiramate, when used for PMEs, may cause a marked decrease in myoclonus and myoclonic seizure frequency, and an improvement in daily functioning (Uldall & Bucholt, 1999). These effects do not appear to be specific to any given PME, but have been particularly studied in LD (Aykutlu *et al.*, 2005; Demir *et al.*, 2013). In one study, however, topiramate efficacy tended to decrease over time and the drug was discontinued in 2 out of 5 patients because of a rapid increase in cognitive impairment and vomiting (Aykutlu *et al.*, 2005).

Zonisamide

Zonisamide, a sulfonamide derivative chemically distinct from any of the previously established AEDs, is indicated for the treatment of refractory partial epilepsy, but is also useful for a variety of generalized epilepsies, including epileptic encephalopathies, such as Lennox-Gastaut and West syndrome.

A number of case reports and small studies have suggested that zonisamide may be effective for treating patients with PME. More specifically, almost all patients with ULD who were treated with zonisamide as add-on therapy showed a dramatic reduction in myoclonus and a marked improvement in generalized tonic-clonic seizures and daily functioning, although this effect may subside over time (Henry *et al.*, 1988; Kyllerman & Ben-Menachem, 1998; Yoshimura *et al.*, 2001).

Tassinari *et al.* (1999) investigated the efficacy and tolerability of zonisamide in the treatment of severely disabling action myoclonus. In the 4 patients with PME (2 with ULD and 2 cryptogenic), the authors observed a dramatic improvement, as documented by video-polygraphic recording of the patients before and at various times after the start of zonisamide therapy.

Vossler *et al.* (2008) used add-on zonisamide (up to 6 mg/kg/die) in 30 patients with a variety of PME syndromes refractory to common AEDs. They found a $\geq$50 per cent decrease in myoclonic seizure frequency, measured over a 24-hour period, in 38 per cent of patients. About half of the patients experienced side effects consisting of anorexia, asthenia, and somnolence.

Italiano *et al.* (2011) carried out a pilot, open-label trial of add-on zonisamide (up to 6 mg/kg/day) in 12 patients with EPM1 and studied the effect on myoclonus by means of the Unified Myoclonus Rating Scale, obtained for each subject before and after zonisamide add-on treatment. The authors observed a significant reduction in myoclonus severity following the introduction of zonisamide, associated with a good tolerability profile.

Lamotrigine

Lamotrigine, a triazine derivative developed from a series of folate antagonists, is a useful medication for a wide variety of epilepsies, including partial and generalized conditions. Its plasma levels are markedly increased by valproate co-administration, an interaction which largely explains the significant increase in lamotrigine potency after the addition of valproate.

The clinical experience with the use of lamotrigine for the treatment of myoclonus has given conflicting results. Wallace (1998) reviewed the effect of lamotrigine on different myoclonic syndromes and concluded that lamotrigine could be useful for the control of myoclonus for a variety of conditions, including PMEs. It was noted to be particularly efficacious for the treatment of seizures (of any type) of infantile and juvenile neuronal ceroid lipofuscinosis (Aberg *et al*., 1999). More recently, lamotrigine was revealed to improve disabling myoclonus in a patient with a mtDNA A3243G mutation (Costello & Sims, 2009).

In juvenile myoclonic epilepsy, however, lamotrigine was reported to exacerbate myoclonus in some cases. A similar effect was reported in some children with Dravet syndrome (Guerrini *et al*., 1998). Genton *et al*. (2006) retrospectively analyzed the effect of add-on lamotrigine in 5 patients with ULD and observed either an aggravation of myoclonic jerks or a lack of improvement. The authors concluded that lamotrigine is not a sensible treatment option for ULD.

Brivaracetam

Following the discovery of the mechanism of action of levetiracetam, which involves a specific binding site on the presynaptically located synaptic vesicle protein, SV2A, great efforts were made to identify molecules which had structural analogy to levetiracetam and showed high binding constants to SV2A. Brivaracetam, a novel molecule with a 10-fold higher affinity for the SV2A binding site than levetiracetam, was proposed as a drug with high potential efficacy for myoclonus, as suggested by preclinical studies in an established rat model of cardiac arrest post-hypoxic myoclonus (Tai & Truong, 2007) and a phase IIa trial in which its efficacy in the photoparoxysmal response model was analyzed for photosensitive epilepsies (Kasteleijn-Nolst Trenité *et al*., 2007). In this study, brivaracetam, administered at a daily dose of 80 mg, eliminated the photoparoxysmal responses in 14/18 patients for a period of time exceeding the half-life of the drug.

In 2005, brivaracetam received orphan drug designation by the European Medicines Agency for development in PME and from the US Food and Drug Administration for the treatment of symptomatic myoclonus. Two prospective, multicentre, randomized, double-blind, placebo-controlled, parallel-group studies of brivaracetam as adjunctive treatment in 50 and 56 patients, respectively, with genetically ascertained ULD have recently been completed (N01187, N01236) (Kälviäinen *et al*., 2009). In the first study, dosages of 50 and 150 mg/day were tested and in the second study, dosages of 5 and 150 mg/day were applied. These patients suffered from moderate-to-severe action myoclonus and were stratified for concomitant use of levetiracetam or piracetam. Both studies failed to reach the primary goal of reducing the severity of action myoclonus, as measured by the Unified Myoclonus rating scale. However, a favourable trend was observed with brivaracetam at a dose of 50 mg/day in the 12-week maintenance period, and a significant improvement in quality of life (measured by QOLIE-31-P) was found with brivaracetam at daily doses of 50 and 150 mg. Moreover, 87 per cent of patients who completed the studies entered the long-term follow-up study. Overall, brivaracetam was well tolerated in this patient population, as evidenced by the high retention rate and the fact that it did not aggravate seizures or myoclonus. The most frequently reported adverse events were dizziness, headaches, and somnolence.

Although these controlled studies did not appear to support significant efficacy of brivaracetam for the treatment of ULD, a number of factors could have biased the results, including the severity and long duration of the disease, the small scale of the patient population, a high inter- and intra-patient variability, and, perhaps most importantly, the fact that many patients were already on high doses of levetiracetam and/or piracetam, which also act on the SV2A vesicles. A considerable number of patients continued to use brivaracetam after the controlled phase of the trial, for over 6 years, which appears to indicate that this compound has some benefits.

Other drugs and procedures

Perampanel, one of the newer AEDs, is a selective non-competitive antagonist of the AMPA-type glutamate receptors and was recently licensed as adjunctive therapy for the treatment of refractory focal-onset seizures (French *et al*., 2012; Krauss *et al*., 2012).

Two reports document its efficacy when used as add-on therapy for the treatment of LD. The first case was a 21-year-old female patient who was administered perampanel at a dose of 8-10 mg, in addition to a regimen that included clonazepam, levetiracetam, piracetam, valproate, zonisamide, a ketogenic diet, and VNS. This therapeutic change resulted in seizure remission for more than 3 months and led to a reduction in the number of epileptiform discharges on EEG (Schorlemmer *et al*., 2013). The second case was a 15-year-old girl who experienced a dramatic decrease in her seizure frequency, as well as improvement in neurological and cognitive function following initiation of treatment with 10 mg perampanel, administered as monotherapy. Perampanel was therefore proposed as the first potentially efficacious treatment for LD (Dirani *et al*., 2014).

In line with the serotoninergic hypothesis of myoclonus, which suggests that serotonergic

hypofunction is involved in the genesis of myoclonus in PMEs and other myoclonic disorders, 5-hydroxy-L-tryptophan, a precursor of serotonin, was used for the treatment of PMEs. In 1980, Koskiniemi *et al*. (1980) performed a double-blind, placebo-controlled, cross-over study with 2 g L-tryptophan in 7 patients with ULD and found a significant improvement in 6 patients, mostly concerning ambulation, myoclonic jerks, and general condition. With long-term L-tryptophan treatment, however, the effect disappeared or was even reversed in 3 of the 7 patients after 3 to 4 weeks. Similar positive short-term results were obtained in a further group of 11 Finnish patients with ULD who received up to 100 mg/kg of L-tryptophan plus carbidopa (in order to prevent metabolism outside of the brain) over a 6-week period (Leino *et al*., 1981). In contrast, Pranzatelli *et al*. (1995) reported no significant change in myoclonus or ataxia evaluation score in a double-blind, cross-over study with L-5HTP in 8 patients with a variety of PME. Overall, this drug does not appear to have a place in the modern treatment of ULD.

N-acetylcysteine is a sulfhydryl antioxidant that increases cellular glutathione and the activity levels of several antioxidant enzymes. Hurd *et al*. (1996) reported marked beneficial effects on mobility, speech, and seizures in at least 2 of 4 severely affected siblings with ULD treated with N-acetylcysteine in combination with other antioxidants (riboflavin, vitamin E, selenium, and zinc).

Antioxidant vitamins and cofactors, including coenzyme Q_{10} and L-carnitine, are empirically used to treat mitochondrial disorders (Shahwan *et al*., 2005; Di Mauro & Mancuso, 2007). Baclofen, a muscle relaxant normally used to treat spasticity by inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, has shown promising results in a few PME cases with prominent spasticity and polymyoclonus (Awaad & Fish, 1995). Ropirinole, a dopamine agonist commonly used to treat Parkinson's disease, was shown to improve myoclonus, writing, and muscular balance in a single patient with ULD (Karvonen *et al*., 2010). Ethosuximide is active against negative myoclonus, which is often found in PMEs, in association with positive myoclonus.

Alcohol was proven to have some beneficial effects in patients with myoclonus by decreasing myoclonic jerks and improving speech and gait (Genton & Guerrini, 1990). This compound, however, can be used only occasionally to improve the quality of a patient's social life; in contrast, regular use can induce the development of tolerance or even dependence.

A high-fat and low-carbohydrate diet (with a ratio of fat to carbohydrate of 3:1 or 4:1), also known as a ketogenic diet, has been shown to be useful for a variety of severe, drug-resistant epilepsies, including infantile myoclonic seizures. An Italian study of 5 patients with LD, a condition which causes a specific glycogen metabolism disorder, showed that a ketogenic diet, though well tolerated, was unable to stop disease progression (Cardinali *et al*., 2006). It is now hypothesized that potential targets of new molecules for LD could involve the inhibition or modulation of glycogen synthesis (Pedersen et al., 2013).

Different *stimulation procedures* have also occasionally been employed for patients with PMEs. Vagal nerve stimulation was implanted in an adult patient with a ULD-type PME, who was followed for 1 year, and the procedure resulted in a marked reduction in seizures (more than 90 per cent) and a significant improvement in cerebellar function, as demonstrated on neurological examination (Smith *et al*., 2000). Chronic high-frequency deep brain stimulation (DBS) of the subthalamic nucleus has been used in an adult patient with an undiagnosed form of PME who was disabled due to frequent seizures, despite vagal nerve stimulation and a complex antiepileptic regimen (Vesper *et al*., 2007). After a 12-month follow-up, the seizures were reduced in intensity and frequency by 50 per cent. More recently, 5 adult patients with PME underwent chronic high-frequency DBS (Wille *et al*., 2011). Electrodes were implanted in the substantia nigra pars reticulata (SNr)/subthalamic nucleus (STN) region in the first patient and additionally in the ventral intermediate nucleus (VIM) bilaterally in the next four cases. After a mean follow-up of 24 months, a reduction in myoclonic seizures was observed in all patients, ranging between 30 and 100 per cent, as quantified by a standardized video protocol. All patients reported clinically relevant improvements of various capabilities, such as free standing, walking, and improved fine motor skills. The best clinical effects were seen with SNr/STN DBS in all patients.

Drugs and circumstances to avoid

Interestingly, rather than being beneficial, some AEDs have the potential to exacerbate myoclonic seizures and should be used with caution in patients with PME (*table 2*). More specifically, sodium channel blockers (carbamazepine, oxcarbazepine, and phenytoin) and GABAergic drugs (vigabatrin and tiagabine), as well as gabapentin and pregabalin, should, in general, be avoided as they may aggravate myoclonus and myoclonic seizures (Medina *et al*., 2005).

Phenytoin has also been found to aggravate neurological symptoms and cerebellar ataxia in ULD and its widespread use in the past has been proposed as an explanation for the poor prognosis of ULD described in the early series reports (Iivanainen & Himberg, 1982; Elridge *et al*., 1983).

Table 2. Antiepileptic drugs and effects on myoclonus in PME.

Antimyoclonic	Potentially aggravating	To be used with caution	Not documented
Valproate	Phenytoin	Lamotrigine	Lacosamide
Clonazepam	Carbamazepine	Valproate for MERRF	Felbamate
Phenobarbital/Primidone	Oxcarbazepine		Rufinamide
Piracetam	Vigabatrin		Ethosuximide
Levetiracetam	Gabapentin		Eslicarbazepine
Topiramate	Pregabalin		
Zonisamide	Tiagabine		

Emergency treatment of PMEs

In situations where myoclonic jerks are exacerbated, leading to a series of jerks or status myoclonicus, loud noises and bright lights should be avoided and the patient should be treated in a quiet room, as calmly as possible. Emergency treatment includes the intravenous use of benziodiazepines (diazepam, lorazepam, clonazepam, and midazolam), valproate, and levetiracetam (Fernandez-Baca Vaca *et al*., 2012). Phenytoin, although usually contraindicated for PMEs, has proven to be useful in selected cases of refractory status epilepticus, particularly when this occurs in the late stages of a variety of PMEs or in the presence of focal status (Riguzzi *et al*., 1997; Kälviäinen *et al*., 2008; Miyahara *et al*., 2009).

Conclusions

The treatment of PME disorders essentially continues to involve the management of seizures and myoclonus, together with palliative, supportive, and rehabilitative measures. The treatment of myoclonus and seizures in PME can prove to be difficult and both tend to be refractory to conventional medications. Available data on the efficacy of drugs are primarily anecdotal or observational based on small groups of patients. It is difficult to conduct controlled clinical trials in these patients because the incidence of these disorders is exceedingly rare; however, collaborative trials involving many specialized centres could be designed to bring together a sufficient number of patients with a genetically verified diagnosis. Following the availability of brivaracetam, a potentially effective antimyoclonic agent, 2 multicentre, randomized, placebo-controlled studies on genetically verified ULD have been performed, but the effect of this drug on action myoclonus was statistically not significant. However, a favourable trend was observed with the 50-mg dose and it was argued that various factors could have negatively influenced the results.

Traditional AEDs used for the treatment of PMEs are valproate, clonazepam, phenobarbital, or primidone. Newer drugs which have been shown to be effective include piracetam, levetiracetam, topiramate, zonisamide, and, possibly, perampanel for LD. Care must be taken to avoid antiepileptic medications that clearly worsen myoclonus, such as vigabatrin, carbamazepine, phenytoin, and gabapentin. Lamotrigine has an unpredictable effect on myoclonus and must be used with caution.

Athough recent advances in molecular genetics have led to the identification of several genes, mutations, and proteins involved in the pathogenesis of PME disorders, therapy targeting the underlying aetiology remains in the experimental phase and results, to date, have not been encouraging. It is expected, however, that future treatments with gene therapy and enzyme replacement, or the identification of drugs that interact with new targets and mechanisms, may help to modify and improve the course of these progressive disorders. □

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