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Movement Disorders (A Videnovich, Section Editor)

Myoclonus: Pathophysiology and Treatment Options

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Opinion statement

Treatment of myoclonus requires an understanding of the physiopathology of the condition. The first step in treatment is to determine if there is an epileptic component to the myoclonus and treat accordingly. Secondly, a review of medications (e.g., opiates) and comorbidities (e.g., hepatic or renal failure) is required to establish the possibility of iatrogenic and reversible conditions. Once those are eliminated, delineation between cortical, cortico-subcortical, subcortical, brainstem, and spinal generators can determine the first-line treatment. Cortical myoclonus can be treated with levetiracetam, valproic acid, and clonazepam as first-line agents. Phenytoin and carbamazepine may paradoxically worsen myoclonus. Subcortical and brainstem myoclonus can be treated with clonazepam as a first-line agent, but levetiracetam and valproic acid can be tried as well. L-5-Hydroxytryptophan and sodium oxybate are agents used for refractory cases. Spinal myoclonus does not respond to anti-epileptic drugs, and clonazepam is a first-line agent. Botulinum toxin treatment can be useful for focal cases of spinal myoclonus. The etiology of propriospinal myoclonus is controversial, and a functional etiology is suspected in most cases. Treatment can include clonazepam, levetiracetam, baclofen, valproate, carbamazepine, and zonisamide. Functional myoclonus requires multimodal and multidisciplinary treatment that may include psychotropic drugs and physical and occupational therapy. Close collaboration between neurologists and psychiatrists is required for effective treatment. Finally, deep brain stimulation targeting the globus pallidus pars-interna bilaterally has been used in myoclonus-dystonia when pharmacological treatments have been exhausted.

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Introduction

Myoclonus is a hyperkinetic movement disorder characterized as a sudden, jerky, shock-like movement. It can involve different body parts individually (focal), contiguously (segmental), or globally synchronously (generalized) or asynchronously (multifocal) [1]. When repetitive, the jerks may be regular or irregular, sometimes mimicking tremor [2]. Positive myoclonus is generated by contraction of muscles due to excitatory inputs, whereas negative myoclonus is defined as the sudden loss of muscle tone (e.g., asterixis) caused by inhibitory inputs [3].

Classification of myoclonus can be based on clinical features, pathophysiology, or etiology, the latter two being most useful for treatment [1] (Table 1). Physiological forms of myoclonus exist, such as hypnic jerks, anxiety, exercise-induced jerks, and hiccups [4]. Furthermore, functional myoclonus is another consideration and is characterized by variability, distractibility, entrainment, and suppressibility of the jerks. They also possess variable latencies from stimulus to myoclonus when there is stimulus sensitivity. Neurophysiology aids in the assessment of these patients include the presence of bereitschaftspotential [1]. Myoclonus may be combined with other movement disorders such as ataxia (opsoclonus-myoclonus-ataxia syndrome), parkinsonism (idiopathic Parkinson's disease, multiple system atrophy, corticobasal degeneration), and dystonia (Wilson's disease, pantothenate kinase-associated neurodegeneration). Progressive cognitive decline, if present in the young, may lead to a diagnosis of progressive myoclonic encephalopathies, whereas if present in older individuals may guide toward a diagnosis of neurodegenerative diseases such as dementia with Lewy bodies or Creutzfeldt-Jakob disease [5••].

A comprehensive discussion of etiological diagnosis of myoclonus is beyond the scope of this article. Key differentials that must be considered are drug-induced myoclonus (Table 2), myoclonus that occur in the context of sepsis or metabolic derangements (e.g., hepatic failure, renal failure, hyponatremia, and dialysis disequilibrium syndrome), since these are reversible upon removal of the offending agent or correction of the underlying metabolic abnormalities. Epileptic myoclonus should be eliminated as this is also treatable, especially epilepsia partialis continua. Finally, infectious etiologies (herpes simplex encephalitis, subacute sclerosing panencephalitis, Whipple disease) or inflammatory etiologies (anti-NMDA receptor antibody encephalitis [6], progressive encephalomyelitis with rigidity and myoclonus [7], and opsoclonus-myoclonus-ataxia syndrome [8, 9]) may have specific anti-infectious or immune-modulating treatments.

This article will focus on the symptomatic treatment of myoclonus according to a segmental classification (Table 3) and will review certain key syndromes that present predominantly with myoclonus.

Pathophysiology

The pathophysiology of myoclonus is different according to the generator sites. The generator of myoclonus may be localized to the cortex, subcortical areas, brainstem, or spinal cord. This approach aids in the differential diagnosis of the etiology of the movement disorder. An important clarification of this classification is that myoclonus physiology may overlap in these anatomical divisions.

Cortical myoclonus is present when the primary motor cortex discharges an uninhibited impulse down the corticospinal pathway. Some evidence implicates the cerebellum in cortical myoclonus whereby decreased inhibitory outputs from the cerebellum via the cerebello-thalamo-cortical pathways are deficient [10]. Cortical myoclonus may be seen at rest (e.g., in epileptic myoclonus), with action (cortical action myoclonus) and with sensory stimulation (stimulus-sensitive myoclonus). The jerks are usually multifocal, usually with predominant distal musculature involvement owing to the large cortical representation of those body regions [4]; however, less commonly focal, segmental, and generalized myoclonus can occur. Electrophysiological elements supporting the presence of cortical myoclonus include the electroencephalogram (EEG) spikes or sharp waves, time-locked cortical transients on EEG-electromyograph (EMG) simultaneous recording, enlarged cortical somatosensory evoked potential waves, and enhanced long latency EMG responses to peripheral nerve stimulation. Jerk-locked EEG-EMG recordings have higher sensitivity to find cortical transients than routine EEGs. These transients last 15 to 40 ms and occur 6–22 ms before the myoclonic jerk. Bereitschaftspotentials (BPs) are cortical potentials seen on jerk-locked back-averaged EEG preceding voluntary movements [11]. The morphology consists of a slow negative EEG deflection starting 0.7 to 2.1 s before the myoclonic jerk. Their presence aids in the identification

Table 1. Anatomical classification of myoclonus and selected etiologies

Anatomical substrate	Etiology	
Cortical	Degenerative cortical disorders	Creutzfeldt-Jacob disease Dementia with Lewy bodies Corticobasal degeneration Alzheimer's disease Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
	Infectious	Subacute sclerosing panencephalitis Herpes simplex encephalitis Whipple disease Postinfectious encephalitis
	Epileptic syndromes	Familial cortical myoclonic tremor with epilepsy Epilepsia partialis continua
	Focal CNS damage	Post-stroke Neoplasia Post-traumatic
Cortical-Subcortical	Degenerative basal ganglia disorders	Progressive supranuclear palsy Parkinson's disease Huntington's disease Neurodegeneration with brain iron accumulation type 1 Corticobasal degeneration Multiple system atrophy SCA 2, SCA14, SCA19, SCA24 Wilson's disease Dentatorubro-pallidoluysian atrophy
	Epileptic syndromes	Juvenile myoclonic epilepsies Childhood absence epilepsy Progressive myoclonic encephalopathies Angelman syndrome Myoclonic epilepsy with ragged-red fibers (MERRF)
	Metabolic	Post-hypoxic myoclonus (Lance-Adams syndrome) Hepatic/renal failure Dialysis syndrome Hyponatremia Hypoglycemia Biotin deficiency Celiac disease Hashimoto encephalopathy
Subcortical	Basal ganglia disorders	Myoclonus-dystonia syndrome
	Toxic	Bismuth Heavy metal poisons Methyl bromide Dichlorodiphenyltrichoroethane (DDT)
	Medication induced	See Table 2
	Autoimmune	Opsoclonus-myoclonus-ataxia syndrome

Table 1. (Continued)

Anatomical substrate	Etiology	
Brainstem		Reticular reflex myoclonus Post-hypoxic (Lance-Adams Syndrome) Fredreich ataxia Ataxia-telangiectasia
Spinal	Spinal segmental	Trauma Inflammation Infection Demyelination Tumor Arteriovenous malformation Ischemic myelopathy Spondylitic myelopathy Spinal anesthesia
	Propriospinal	Trauma Tumor Functional

of functional myoclonus [12•, 13] and jerky movement disorders [14]. P25-N33 SEPs are enlarged or giant in cortical myoclonus (with or without reflex activation), being respectively >11 to 20 μV, depending on reference values for each laboratory. Reflex myoclonus can be elicited clinically by muscle stretch or by peripheral nerve stimulation. Peripheral nerve stimulations (usually the median nerve) generate myoclonic responses recordable with surface EMG at a latency ranging from 40 to 60 ms in hand muscles. This response should be absent in a normal individual at rest. Generalized or bilateral myoclonus of cortical etiology occurs when intrahemispheric or interhemispheric spread occurs. The myoclonic jerks may look synchronous; however, electrophysiologically, this is not the case.

Asterixis, or negative myoclonus, is clinically characterized by a sudden loss of muscle tone and is usually multifocal and asynchronous. Both positive and negative myoclonus can coexist in the same patient. The generator may be located in cortical or subcortical structures. On EMG recordings, the electrical silence lasts between 50 and 200 ms, with a variably present EEG signal.

Epileptic myoclonus usually originates in the cortex but may involve subcortical structures. Focal motor seizures may present as myoclonus in isolated paroxysms or sustained jerks in epilepsia partialis continua. On the other hand, epileptic myoclonus in generalized myoclonic epilepsies involves a bidirectional oscillation between cortical and subcortical structures with each structure driving the other [15]. EMG burst duration is less than 100 ms.

Subcortical myoclonus typically involves many muscle groups with widespread distribution. Predictably, the absence of signs of cortical excitability on EEG (e.g., cortical spikes and giant somatosensory evoked potentials) supports the localization to the subcortex. Burst duration may be longer than those in cortical myoclonus, ranging from 75 to 300 ms.

In reticular (brainstem) reflex myoclonus, there may be myoclonus at rest and reflex jerks that originate from the medullary reticular formation. Reflex myoclonus may occur to tactile, muscle stretch, deep tendon reflex, or auditory stimuli. Contrary to cortical myoclonus, axial and proximal limb activation occurs preferentially. Brainstem reflex myoclonus may also have short EMG durations of less than 100 ms. Hyperekplexia, with excessive startle response, is a special form of brainstem myoclonus. It is an autosomal dominant condition caused by a mutation in the gene for glycine receptors. Glycine is an inhibitory neurotransmitter in the brainstem and spinal cord. This inhibitory signal is deficient in hyperekplexia.

Segmental myoclonus involves contiguous segments of the spine or brainstem with rhythmical activation of those muscles, unaffected by changes in the level of consciousness [15]. Pathologically, there is loss of spinal inhibitory interneurons which results in spontaneous

Table 2. Drug that may induce myoclonus

Class	Drug
Antiparkinsonian	Amantadine Levodopa Bromocriptine Entacapone
Antidepressant drugs	Tricyclic antidepressants Selective serotonin reuptake inhibitors Monoamine oxidase inhibitors Lithium
Anxiolytics	Buspirone Lorazepam Midazolam Benzodiazepine withdrawal
Dopamine receptor-blocking agents	Neuroleptics Clozapine Metoclopramide
Antiepileptic drugs	Valproic acid Carbamazepine Phenytoin Gabapentin Lamotrigine
Analgesics	Opiates intravenous or intrathecal Fentanyl, methadone, meperidine, hydrocodone
Chemotherapy	Chlorambucil Prednimustine Busulfan with cyclophosphamide Ifosamide
Antibiotics and antivirals	Penicillin Ticarcillin Cephalosporins Imipenem Piperacillin Quinolones Isoniazid Acyclovir
Cardiovascular drugs	Propafenone Flecainide Diltiazem Nifedipine Amiodarone
Anesthetics	Propofol Etomidate Enflurane

firing of anterior horn cells [1]. Stimulus sensitivity and voluntary action enhancement of these jerks rarely occur. Synchronous activation of muscles in the same segment is observed on EMG with burst frequency varying between 50 and 500 ms. Predictably, there is absence of electrophysiological involvement of cortical structures.

Table 3. Treatment of myoclonus according to anatomical sites

Anatomical substrate	Treatment options		Rarely effective	Paradoxical worsening
	First line	Second line		
Cortical	Levetiracetam	Topiramate	Primidone	Phenytoin
	Valproate	Zonisamide	Pheobarbital	Carbamazepine
	Clonazepam	Sodium oxybate		Lamotrigine
	Piracetam			
Cortical-subcortical	Levetiracetam	Ethosuximide		Carbamazepine
	Valproate			Phenytoin
	Topiramate			
	Lamotrigine			
	Piracetam			
Subcortical	Levetiracetam	Sodium oxybate		Meperidine
	Valproate	L-5HTP		Amantadine
	Clonazepam			
	Piracetam			
Brainstem	Levetiracetam	L-5HTP		
	Clonazepam			
	Valproate			
	Piracetam			
Spinal	Clonazepam	Levetiracetam	Tetrabenazine	
	Diazepam	Botulinum toxin injections	Sodium oxybate	

Treatment

Physiologic myoclonus

- Physiologic myoclonus may occur in normal circumstances in patients without neurological disease [1]. The most common is hypnic myoclonus, occurring at transitions to and from sleep. Considering the benign nature of this phenomenon, treatment is not warranted, although bed partners may be disturbed by these movements more so than patients themselves. When these jerks do become bothersome, clonazepam may be used as treatment [16]. Care should be taken to differentiate these movements from periodic leg movements of sleep (occurring during non-REM sleep) and from manifestations of epilepsy [17].

Metabolic and toxic etiologies

- This class of etiologies requires mention since they are usually reversible with correction of the underlying metabolic disorder or removal of

offending agent. Firstly, hepatic encephalopathy is a clear cause of negative myoclonus (asterixis), which may be present even in the early stages of the encephalopathy [18]. Myoclonus in the setting of renal failure can be multifactorial. Uremia itself can cause myoclonus; however, addition of medications in this setting can combine drug-induced etiologies. Examples include acyclovir, dobutamine, ciprofloxacin, and cephalosporins [5••]. Dialysis disequilibrium, another induced cause of myoclonus, occurs during intermittent dialysis and is related to abrupt shifts in water and aluminum content in the dialysate [5••, 18]. In the setting of renal failure, myoclonus may be present with a range of encephalopathy from mild irritability to overt delirium.

- Examples of drugs inducing myoclonus are shown in Table 2. A careful review of recent changes or additions of medications is warranted since combinations of drugs may produce myoclonus at lower doses. All these etiologies are of presumed cortical-subcortical origin and thus present with multifocal action or stimulus-sensitive myoclonus. Furthermore, other neurological manifestations may be present such as seizures, encephalopathy, and hallucinations which provide clues to these reversible etiologies [19]. In the event that offending medications cannot be withdrawn, addition of an anti-myoclonic agent (see below) can be considered [20].

Pharmacologic treatment

Cortical myoclonus

- Etiologies of cortical myoclonus are summarized in Table 1. There are no formal guidelines for symptomatic treatments of myoclonus. Owing to the increased cortical excitability generating the myoclonus, some antiepileptic agents are effective treatments (Table 3). However, phenytoin, carbamazepine, and lamotrigine produce paradoxical worsening of myoclonus. Primidone and phenobarbital are rarely effective [5••].
- Early post-hypoxic myoclonus occurs within 48 h of cardiopulmonary arrest, usually when prolonged hypoxia predates the cardiac arrest. It presents as multifocal cortical myoclonus with the patients is in an altered mental state. Seizure activity should be ruled out in these cases.
- Progressive myoclonic encephalopathies are a set of conditions with cortical myoclonus. They present with progressive encephalopathy with onset in childhood or youth. There is association of myoclonus with seizures, ataxia, hallucinations, and cognitive impairment. The most common disease is Unverricht-Lundborg disease, caused by a mutation in EPM1.

Piracetam

Standard dosage	2.4 g tid (initial doses), 5.6 g tid (usual dose), 8 g tid (maximal dose).
Contraindications	Requires adjustment for creatinine clearance.

Main drug interactions	Since piracetam is renally excreted, there are little interactions with hepatically metabolized drugs.
Main side effects	Diarrhea, weight gain, somnolence, insomnia, nervousness, depression, rash are rare.
Special points	Piracetam is an analog of levetiracetam. It has been studied in a randomized double-blind placebo-controlled crossover study finding a statistically significant clinical effect [21] (class II). Another observational study in different forms of myoclonus showed that 16/40 patients improved clinically with the addition of piracetam to their ongoing anti-myoclonic treatment [22]. The patients that improved had cortical myoclonus, whereas those with cortical reflex myoclonus did not respond. In Unverricht-Lundborg disease, it was also shown to be efficient in a placebo-controlled trial of three different doses [23].
Cost/cost-effectiveness	Medication not available in the USA or Canada. Relatively inexpensive.

Levetiracetam

Standard dosage	500–1000 mg bid (starting doses), 1000–2000 mg per day usually required.
Contraindications	Requires adjustment for creatinine clearance.
Main drug interactions	Since levetiracetam is renally excreted and hepatic metabolism is minimal, this drug is not affected by medications affecting CYP450 enzymes.
Main side effects	CNS depression, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been reported. Psychiatric disturbances (irritability, psychosis, paranoia, and behavioral issues) may be less frequent than commonly thought and a recent meta-analysis cites 1 % of patients experiencing this compared to placebo [24].
Special points	This anti-epileptic drug is generally well tolerated and effective for cortical myoclonus arising from stroke, neurodegenerative diseases, and epileptic etiologies [25–27] (class III). In the case of post-hypoxic myoclonus (Lance-Adams syndrome), levetiracetam can result in dramatic improvement of the action-induced component of the myoclonus of the upper limbs more so than the more prominent negative component of the lower limbs.
Cost/cost-effectiveness	Keppra™ $8.31 US/tablet, levetiracetam $3.51 US/tablet (500 mg tablets) [28]

Valproic acid

Standard dosage	250 mg bid (starting doses), 750–1000 mg bid usually required (monotherapy).
Contraindications	Patients with hepatic disease should not receive valproic acid. Furthermore, those with neurometabolic mitochondrial diseases should avoid this drug since it can cause acute liver failure. Finally, there is a clear teratogenic risk (mainly spina bifida) in patients taking valproic acid and should be avoided in women of childbearing age.
Main drug interactions	Valproic acid is hepatically metabolized and is both an enzyme inhibitor and inducer. Care should be taken to review medication interactions especially with other anti-epileptic drugs.
Main side effects	Although safe and well tolerated, valproic acid has side effects that limit its use. Life threatening pancreatitis, hepatic failure, thrombocytopenia and drug reaction with eosinophilia and systemic symptoms (DRESS) can occur. Other androgenic side effects are weight gain, hirsutism, and hair loss. Tremor occurs in about 50 % of cases.

Special points	No comparative study has been between levetiracetam and valproic acid, but the side effect profile of the former is may be more favorable.
Cost/cost-effectiveness	Depakene™ $4.04 US/tablet, valproic acid $0.83 US/tablet [28].

Clonazepam

Standard dosage	0.5 mg tid (initial dosing), effective dose as high as 5 mg tid.
Contraindications	Patients with significant baseline sedation or other sedating medications should introduce the medication gradually.
Main drug interactions	None.
Main side effects	Sedation.
Special points	The sedative effect of benzodiazepines limits their use since high doses are often required for adequate control. Clonazepam may be more useful as an adjunctive medication with other non-sedating medications such as levetiracetam or valproic acid. Furthermore, clonazepam is not exclusively used for cortical myoclonus; subcortical and segmental myoclonus being responsive to this drug (see below).
Cost/cost-effectiveness	Clonazepam $0.75 US/tablet (0.5 mg) [28].

Topiramate

Standard dosage	25 mg bid (initial dose), 75–100 mg bid (therapeutic doses).
Contraindications	Caution should be used in patients with a history of renal lithiasis.
Main drug interactions	Caution with hepatically metabolized drugs.
Main side effects	Sedation, reversible cognitive dysfunction (psychomotor slowing, concentration difficulties), renal lithiasis, closed angle glaucoma, weight loss.
Special points	Topiramate is another add-on option for progressive myoclonic epilepsies, but as monotherapy may be less effective.
Cost/cost-effectiveness	Topiramate $2.55 US/tablet (25 mg) [28]

Zonisamide

Standard dosage	100 mg qd (initial), 200 mg qd (therapeutic dose)
Contraindications	Care with hepatic impairment, contraindicated in patients with severe renal failure, cross reactions with sulphonamide allergies.
Main drug interactions	Since zonizamide is hepatically metabolized (CYP3A4), care should be taken with medications that effect hepatic metabolism.
Main side effects	Sedation, psychomotor slowing (higher doses), metabolic acidosis.
Special points	Evidence exists for add-on efficacy with progressive myoclonic epilepsies (Unverricht-Lundborg disease and Lafora body disease)
Cost/cost-effectiveness	Zonegran $13.98 US/tablet (100 mg), zonisamide $2.19 US /tablet (100 mg) [28]

Subcortical myoclonus

- Subcortical myoclonus represents a heterogeneous group of disorders. In particular, hereditary causes are included in here. The most pertinent

one is myoclonus-dystonia (DYT11), associated with mutations of *SGCE* coding for sarcoglycan epsilon. A consistent feature of this condition is its striking alcohol sensitivity; and therefore benzodiazepines (e.g., clonazepam) produces a reliable effect. Myoclonus phenomenology may include proximal body segments (upper arms and trunk). The dystonic phenomenology may be limited to focal writing dystonia and responds to anticholinergic medications (e.g., trihexyphenidyl).

- In addition to the specific medications listed below, clonazepam, levetiracetam, piracetam, valproic acid, and topiramate are all potentially effective in treating subcortical myoclonus.
- Late post-hypoxic myoclonus (Lance-Adams syndrome) is a subcortical brainstem-induced myoclonus with an onset of days to weeks from the index event, in contrast to early post-hypoxic myoclonus described above. The patient is fully conscious but may have residual cognitive dysfunction [5••, 29]. The muscle jerks are triggered by movement, startle of tactile stimuli, and can be very debilitating. The physiopathology of Lance-Adams syndrome is unknown; but there is deficiency in serotonin of which L-5-hydroxytryptophan (L-5HTP) is a precursor and of GABA (see below). Levetiracetam, clonazepam, and valproic acid are useful first-line options to treat this condition. L-5HTP and sodium oxybate are both rescue therapies.
- Paradoxical worsening of subcortical myoclonus can be seen with meperidine and amantadine.

Sodium oxybate (gamma hydroxybutyrate)

Standard dosage	1 g qd (initial dose), 3 g tid (maintenance dose) [26; 30] (class IV).
Contraindications	Care should be taken when using sodium oxybate and other sedative medications such as benzodiazepines.
Main drug interactions	None.
Main side effects	Sedation is a significant side effect reported. Serious side effects such as obtundation and respiratory depression may occur with overdose. Furthermore, amnesia may occur.
Special points	Sodium oxybate is derived from GABA and enhances inhibitory neurotransmission. It is therefore effective in alcohol-sensitive myoclonus (DYT11) [26, 31]. Furthermore, it has also been reported to be effective in late post-anoxic myoclonus [32]. The difficulty using this medication is its potential for abuse and restricted access.
Cost/cost-effectiveness	Xyrem oral $45.22 US/g [28]

L-5-Hydroxytryptophan

Standard dosage	100 mg qid (initial dose), 400–500 mg qid (typical dose, requiring slow taper).
Contraindications	None.
Main drug interactions	None.
Main side effects	L-5-Hydroxytryptophan is a precursor to serotonin. Diarrhea, flushing, and persistent euphoria are typical side effects.

Special points This medication is not readily available and thus less used [33, 34] (class IV). Multiple times a day dosing requires careful compliance, and peripheral serotoninergic side effects can be bothersome. The addition of carbidopa (a peripheral decarboxylase inhibitor) 50 mg qid can limit these side effects. Despite these limitations, adequate control can be achieved when first-line medications have failed or in combination with them.

Cost/cost-effectiveness Not marketed, requires special access from health agency. Relatively inexpensive.

Brainstem myoclonus

- Clinically, two forms of brainstem myoclonus exist.
- Hyperekplexia is due to exaggerated startle reflex and presents clinically as an exaggerated, non-habituating, response to unexpected auditory, tactile, and visual stimuli. Babies with this condition are hypertonic and stiff. Minor manifestations can be excessive startle and hypnic jerks. Clonazepam and sodium valproate can be effective treatments [1].
- Reticular (brainstem) reflex myoclonus occurs with post-anoxic encephalopathy and can be treated with the same agents as Lance-Adams syndrome. Levetiracetam can be particularly useful with the action component of the myoclonus.
- Opsoclonus-myoclonus-ataxia syndrome is an autoimmune disorder that can be part of a pediatric or an adult syndrome. One defining characteristic is opsoclonus, which are chaotic myoclonic ocular movements. When the syndrome is found in children, it is part of a paraneoplastic syndrome secondary to either a neuroblastoma or a ganglio-neurobalstoma. In adults, opsoclonus-myoclonus-ataxia syndrome is predominantly idiopathic, post-infectious, or associated with autoimmune encephalitis (e.g., anti-NMDA receptor encephalitis). When it is associated with a paraneoplastic syndrome, anti-Ri antibodies are most commonly found and the primary tumor is most frequently a small cell lung carcinoma. Treatment is a combination of anti-neoplastic treatment as needed and immunotherapy [5••, 9].
- Palatal myoclonus is now reclassified as a tremor, owing to its electrophysiology and clinical features [5••, 35, 36]. Structural brainstem etiologies in the dentate-inferior olive pathway can be found in secondary palatal tremor but not essential palatal tremor. Functional etiologies may explain some cases of essential palatal tremor [37], and it has been successfully treated with patient cueing [38•]. Symptomatic palatal tremor can be treated with anti-epileptic drugs such as phenytoin, carbamazepine, lamotrigine [39], clonazepam, or diazepam. Other medications that have been tried are tetrabenazine or baclofen [1]. There is evidence for use of botulinum toxin injections performed by trained otolaryngologists [40].

Spinal segmental myoclonus

- Most causes of spinal (segmental) myoclonus in Table 1 have a structural etiology but non-lesional cases exist. Known etiologies include spinal cord injury, demyelinating diseases, and herpes myelitis.

- Clonazepam [1, 41] is usually helpful for this form of myoclonus and is the first-line oral medication. Other medications that can be tried are levetiracetam [42], topiramate [43], tetrabenazine, and valproic acid [1]. A case report of two patients reported efficacy for the use of intrathecal baclofen [44].
- If the myoclonus is limited to a certain myotome, botulinum toxin injections can be helpful and limit systemic side effects [45, 46].

Botulinum toxin injections

Standard dosage	Variable dosage depending of toxin formulation and muscles injected.
Contraindications	Hypersensitivity to botulinum toxin is a contraindication.
Main drug interactions	None.
Main side effects	Side effects vary depending on localization of the injection. When using botulinum toxin injections for essential palatal tremor, dysphagia may be a side effect. This can be mitigated by starting at a low dose and gradually increasing at subsequent visits, based on patient tolerance. Rarely, systemic side effects such as xerostomia, blurry vision, and weakness may occur.
Special points	There are case reports for treatments of segmental myoclonus involving limbs [45, 46] (class IV) and abdominal muscles [47] (class IV).
Cost/cost-effectiveness	OnabotulinumtoxinA (Botox) 100 unit vial $669.60 US [28]

Propriospinal myoclonus

- Propriospinal myoclonus is characterized by flexor truncal jerks with an ascending and descending propagation along the spinal cord [48, 49]. This repetitive and arrhythmic myoclonus involves the trunk, neck, knees, and hips, propagating along the spinal cord at a speed of 4–8 m/s [12•]. Typically, the movement is triggered by action but worsens when the patient lies flat or sits and is associated with a premonitory sensation. When an etiology is found they are structural, such as myelopathy due to multiple sclerosis, disk herniation [50], or infectious from herpes zoster, human immunodeficiency virus, Lyme disease, and possibly vascular myelopathy from *Escherichia coli* O157:H7 [51].
- Recent literature has contested the etiology of idiopathic and symptomatic causes of propriospinal myoclonus. Some have reported that diffusion tensor imaging may be more sensitive to microstructural spinal cord lesions in idiopathic cases [12•]. However, clinical diagnosis is unreliable and the presence of bereitschaftspotentials was found in 86.1 % of a cohort of 65 patients with electrophysiological evidence of propriospinal myoclonus [52••]. A review of all published cases estimated that as much as 58 % of all cases may be functional with as little as 7 % of total cases being related to a secondary etiology [13].

- Treatment with clonazepam was helpful in between 60 and 75 % of cases (class IV) [12•]. Other pharmacologic treatments have included baclofen, valproate, carbamazepine, zonisamide, and levetiracetam [12•]. One case report which did not include electrophysiological appraisal of the movements reported use of transcutaneous electric nerve stimulation with good benefit. However, the authors of the case report did question a psychosomatic contribution [53].

Functional (psychogenic) myoclonus

- Functional myoclonus accounts for 5–20 % of functional movement disorders [54, 55]. Besides focal or segmental myoclonus, propriospinal myoclonus and essential palatal tremor (myoclonus) have also been ascribed to a functional etiology [12•, 13, 35–37].
- Treatment of functional movement disorders is difficult and relapses are common. There are methodological limitations in the treatment studies. Mainly, the diagnostic certainty is not always clear and overlap between functional and organic causes is common. Furthermore, there is little literature targeting specifically myoclonus. Treatment modalities include a multimodal and multidisciplinary approach including psychotropic drugs, physical therapy, and occupational therapy. When a comorbid psychiatric condition exists, treatment is warranted and conjoint follow-up between neurologists and psychiatrists is helpful.
- A small randomized trial of early versus delayed psychodynamic psychotherapy in 15 patients demonstrated a mild improvement of the abnormal movements with duration of treatment, rather than treatment allocation. The conclusion was that observation time rather than either intervention determined response [56•] (class II]). A single blind study of 10 patients found improvement in abnormal movements, anxiety, and depression with psychodynamic psychotherapy [57] (class IV).
- The role of physiotherapy was assessed in a large historical cohort study in 60 patients [58] (class IV). This study assessed the benefit of an intensive 1-week rehabilitation program based on motor reprogramming to unlearn the motor pattern involved in functional movement disorders. There was short-term improvement in 68.8 % of patients and long-term improvement in 60.4 % of patients. Three times a week low intensity exercise was assessed in another study which showed improvement of 70 % in the psychogenic movement disorder rating scale after 12 weeks [59]. Combination cognitive behavioral therapy with inpatient physical therapy for functional gait disorders showed improvement of functional independence and mobility [60].
- Patients should be referred to physical therapists with experience in functional movement disorders and with a clear understanding of the objectives of the therapy. Unfortunately there is little training, support,

and knowledge in treatment of this condition in the physical therapy community [61].

Surgical treatment

Deep brain stimulation

- The main surgical treatments for myoclonus involve deep brain stimulation. The selected targets vary and the evidence for each is limited to case reports.
- Considering myoclonus is a symptom and may underlie different etiologies, tailoring DBS to the symptom is difficult.
- Overall, the complications of deep brain stimulation are hemorrhage at the surgical site and transient confusion. Infections, seizures, and pulmonary embolism were also reported [62]. Hardware issues can require lead or stimulator replacement. Furthermore, during initial programming, paresthesias and other transient symptoms may occur.
- No evidence exists for DBS treatment of brainstem or spinal segmental myoclonus.

Cortical myoclonus

Standard procedure	Thalamic DBS (ventral intermediate nucleus-ventral caudalis nucleus border). Globus pallidus pars-interna DBS.
Contraindications	
Complications	No complications were reported in the published literature.
Special points	One case report exists in a patient with post-anoxic myoclonus [63] (class IV). However, the pathophysiology of post-anoxic myoclonus may not exclusively be linked to cortical regions and this case report did not include any neurophysiological classification of the myoclonus confirming a cortical etiology. Furthermore, in this report, myoclonus was bilateral, asymmetric, and predominantly action induced. A second case reported improvement in myoclonus in Lance-Adams syndrome with a prominent action component [64]. Cortical etiology was not confirmed with back-averaged jerk-locked EEG.
Cost/cost-effectiveness	Overall, there is little physiological or clinical evidence to pursue DBS in cortical myoclonus.

Subcortical myoclonus

Standard procedure	Thalamic DBS (ventral intermediate nucleus). Bilateral globus pallidus pars-interna DBS.
Contraindications	
Complications	
Special points	Myoclonus-dystonia is the syndrome for which the most evidence exists for the use of DBS; however, there are no controlled trials available [65–68]. A review of 40 cases revealed that 93.5 % of patients studied demonstrated at least 50 % improvement in myoclonus compared to pre-surgery. Comparison between thalamic targets versus pallidal targets demonstrated no statistical difference between targets on myoclonus. However, the authors noted that dystonia

improved significantly with the pallidal DBS compared to the thalamic target [69••] (class IV). A case report of two patients without a mutation in epsilon sarcoglycan gene showed that both myoclonus and dystonia improved after bilateral pallidal DBS [70] (class IV).

Compliance with Ethical Standards

Conflict of Interest

Ariel Levy declares no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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