Medical Management of Myoclonus-Dystonia and Implications for Underlying Pathophysiology

Conor Fearon MB, PhD[1], Kathryn J Peall MD, PhD[2], Marie Vidailhet, MD, PhD[3,4,5], Alfonso Fasano MD, PhD[6,7,8]

[1]Dublin Neurological Institute at the Mater Misericordiae University Hospital, Dublin, Ireland.

[2]Neurosciences and Mental Health Research Institute, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK, CF24 4HQ

[3]AP-HP, Hôpital Salpetriere, Department of Neurology, F-75013, Paris, France

[4]Institut du Cerveau et de la Moelle, ICM, F-75013, Paris, France.

[5]INSERM U1127, F-75013, Paris, France; CNRS UMR 7225, F-75013, Paris, France; Sorbonne Unversité, F-75013, Paris, France;

[6]Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital – UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada.

[7]Krembil Research Institute, Toronto, Ontario, Canada

[8]Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, ON, Canada

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Corresponding author:

Dr. Alfonso Fasano, MD, PhD

Professor - University of Toronto

Clinician Investigator - Krembil Research Institute

Movement Disorders Centre - Toronto Western Hospital

399 Bathurst St, 7McL412

Toronto, ON Canada M5T 2S8

Fax +1 (416) 603-5004

e-mail: alfonso.fasano@uhn.ca, alfonso.fasano@gmail.com

Abstract

Myoclonus-dystonia is an early onset genetic disorder characterised by subcortical myoclonus and less prominent dystonia. Its primary causative gene is the epsilon-sarcoglycan gene but the syndrome of "myoclonic dystonia" has been shown to be a heterogeneous group of genetic disorders. The underlying pathophysiology of myoclonus-dystonia is incompletely understood, although it may relate to dysfunction of striatal monoamine neurotransmission or disruption of cerebellothalamic networks (possibly via a GABAergic deficit of Purkinje cells). A broad range of oral medical therapies have been used in the treatment of myoclonus-dystonia with a varying response, and limited data relating to efficacy and tolerability, yet this condition responds dramatically to alcohol. Few well conducted randomized controlled trials have been undertaken leading to an empirical ad hoc approach for many patients. We review the current evidence for pharmacological therapies in myoclonus-dystonia, discuss implications for underlying pathogenesis of the condition and propose a treatment algorithm for these patients.

Introduction

Myoclonus-dystonia (M-D) is an early onset genetic disorder characterised by subcortical myoclonus and less pronounced dystonia [1,2]. The myoclonus most commonly affects the upper body and is more prominent with action. Cervical dystonia or writer's cramp may be present, although a wider phenotypic spectrum has been observed [3,4]. Psychiatric comorbidities are associated, in particular obsessive compulsive disorder (OCD) and anxiety disorders [5]. Onset is typically in the first or second decade. The primary causative gene is the epsilon-sarcoglycan gene (*SGCE*), located on chromosome 7q21 [6]. The underlying pathophysiology is incompletely understood, although it may relate to basal ganglia monoaminergic dysfunction [7–9] or disruption of cerebellothalamic networks (possibly via a GABAergic deficit of Purkinje cells) [10].

Disease-modifying treatments for M-D are lacking. For severe forms of the condition, deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) has been shown to be safe and effective, with sustained benefit [11,12]. However, some patients may be ineligible for or refuse surgery. On the other hand, oral medications typically have a variable response in M-D, with poor tolerability limiting their use in many patients. However, a characteristic feature of the disorder is its dramatic alcohol responsiveness [13], implying a pharmacological effect not seen in many other dystonias.

We review the current evidence for pharmacological therapies in M-D and discuss implications for underlying pathogenesis of the condition. A literature search was performed using Medline from January 1979 to December 2019 using the search terms: 'myoclonus'; 'dystonia'; and 'myoclonic dystonia' and combined with a search for terms: 'treatment'; 'therapy'; and 'medication'. Only English-language publications were considered. In addition, systematic checking of references from review articles and other reports was performed as well as a detailed search of ongoing clinical trials at www.clinicaltrials.gov.

Historically, what has been referred to as M-D (and "essential myoclonus") has now been shown to be a genetically heterogenous group of disorders [10,14]. There are a number of conditions which can cause myoclonus and dystonia but whose phenotypes differ from those caused by mutations of *SGCE*. In keeping with what has been recently proposed [10], we will clearly distinguish treatment of these "myoclonic dystonias" from true M-D related to *SGCE* mutations. Menozzi et al. have recently reviewed the relevant genetic causes of myoclonic dystonia [14]. These include *ADCY5* [15]*, ANO3* [16]*, GCH1* [17]*, GNAL* [18]*, GNB1* [19]*, KCTD17* [20]*, NKX2-1* [21]*, PRKCG* [22]*, TH* [23]*, TTPA* [24]*, TUBB2B* [25]. Whereas some phenotypic clues might raise suspicion for a non-*SGCE* myoclonic dystonia (e.g. truncal action dystonia or coexistence of myoclonus and dystonia in the same body part [26], mild delayed motor development with *KCTD17* mutations [20,27], facial myoclonus and orolingual dyskinesia in *ADCY5* [15]), genetic confirmation of *SGCE* mutations are required to interpret outcomes of therapeutic studies in M-D. Some of the early papers were published prior to the discovery of *SGCE* and we will consider the patients therein reported as myoclonic dystonias, even though these series were probably enriched with M-D cases as well. The conclusions drawn from studies on myoclonic dystonia may not, therefore, be fully applicable to M-D. Finally, we will also propose a treatment algorithm for patients with M-D.

Zonisamide

The only medication for which there is class I evidence in the treatment of M-D is zonisamide [28]. Hainque et al. showed in a randomized, double-blind, placebo-controlled crossover trial of 24 patients that zonisamide (300 mg/day) improves both myoclonus and dystonia, along with their associated disability. There were no excess side effects and, in particular, no marked worsening of symptoms in those with co-morbid psychiatric symptoms. However, some study patients did experience mood swings and thus, clinicians are advised to be observant of fluctuations to mood given the underlying predisposition to psychiatric comorbidities seen in this population. One patient enrolled in this trial had to discontinue treatment, despite beneficial effect on motor symptoms, due to impulsivity and mood disorder after 2 months on zonisamide at a dose of 300mg/day (*personal communication of the authors of this*

trial). Zonisamide, a benzisoxazole derivative, acts in a number of ways, including inhibition of voltage-gated sodium channels, inhibition of T-type calcium channels and modulation of GABAergic, glutamatergic and dopaminergic neurotransmission. It is approved in many countries for the treatment of epilepsy but has been employed in other conditions such as Parkinson's disease, essential tremor, cortical and propriospinal myoclonus. Its efficacy in this study suggests that zonisamide is also effective in treating the subcortical myoclonus seen in M-D, although the exact mechanism of action is unclear. It is notable, however, that the voltage-gated T-type calcium channels are expressed in abundance in cerebellar Purkinje cells, deep cerebellar nuclei, basal ganglia (including GPi) and ventral thalamus [29]. Blockade of these channels suppresses summation of excitatory post-synaptic potentials which may explain the mechanism of action of zonisamide in M-D [30].

Other antiepileptic medications

Several other antiepileptic medications have been trialled in patients with myoclonic dystonias including valproate, topiramate, levetiracetam, gabapentin and barbiturates [2,31–34]. Valproate is effective in reducing myoclonus in M-D [35,36], but others such as gabapentin can worsen myoclonus [7], In spite of its efficacy in cortical myoclonus, levetiracetam appears to have limited efficacy in treatment of M-D [37], The efficacy of anti-epileptic drugs is variable in patients with M-D and probably relies on a generic anti-myoclonic effect of the medications rather than a disease-specific action, although valproate may increase GABA levels.

Moghaddam et al. recently reported a seven year-old girl with M-D in whom carbamazepine was successfully employed as therapy [38]. This patient was previously trialled on clonazepam and tetrabenazine, which were found to be ineffective, and levetiracetam which worsened her lower limb dystonia, thus highlighting the delicate balance between improving certain aspects of the disorder while trying to avoid exacerbating others. Carbamazepine was tried as an alternative diagnosis of paroxysmal kinesigenic dyskinesia was considered, and a dramatic improvement in both dystonia and myoclonus was seen. Carbamazepine is a voltage dependent sodium channel antagonist which can exacerbate cortical myoclonus [39]

but may improve peripheral myoclonus [40]. It is possible, therefore, that it can also improve the subcortical myoclonus seen in M-D. There is evidence that carbamazepine increases extracellular serotonin levels (via enhanced release and decreased uptake) and increases dopamine release in the basal ganglia [41,42]. As mentioned above, serotoninergic and dopaminergic systems may play a central role in the generation of myoclonus and dystonia in M-D. Thus, it is conceivable that alteration in one or both of these monoamines is the mechanism by which carbamazepine worked in this patient. A similar response to carbamazepine has been observed in patients with dopa-responsive dystonia suggesting that enhanced dopamine release may be the dominant mechanism [43].

Benzodiazepines

Benzodiazepines, in particular clonazepam (1.5mg-10mg/day), have long been shown to improve myoclonus and tremor in myoclonic dystonias [2,4,44,45]. Benzodiazepines enhance the effect of GABA at the GABA-A receptor, and GABAergic deficits reflecting cerebellar Purkinje cell dysfunction have been implicated in the pathogenesis of M-D [10]. Alcohol transiently enhances GABAergic transmission which may explain the motor symptom improvement observed In M-D. Neurophysiological improvements in dysfunctional cerebellar-dependent associative learning with alcohol have also been demonstrated, and associated with an underlying GABAergic deficit, possibly within cerebellar Purkinje cells [13].

Zolpidem, an imidazopyridine agonist, which also has a high affinity for and positively modulates the BZ1 subtype of GABA-A receptors, led to dramatic improvements one hour after ingestion in a patient with an *SGCE*-negative myoclonic dystonia syndrome who failed to respond to multiple therapies, including diazepam [46]. The highest density of zolpidem-binding GABA-A receptors is found in the ventral globus pallidus, the substantia nigra pars reticularis and the subthalamic nucleus. The authors, therefore, postulated that zolpidem may help restore basal ganglia output influence on the thalamus and motor cortex.

Anticholinergic agents

In a similar manner to benzodiazepines, anticholinergics (such as trihexyphenidyl or benztropine) have been used to treat myoclonic dystonias and may improve both myoclonus and dystonia [2,4,44,47,48]. Response is usually moderate but Lee at al. reported a 19-year-old M-D patient whose myoclonus and dystonia responded dramatically to trihexyphenidyl 6mg/day. This was discontinued after 7 years, with sustained amelioration of both myoclonus and dystonia [49]. Anticholinergic drugs are frequently used in the treatment of other forms of dystonia and, although the exact mechanism of action remains unclear, they may restore the imbalance between striatal dopamine and acetylcholine [50].

Dopaminergic agents

The role that dopaminergic mechanisms play in M-D appears to be complex. Epsilon-sarcoglycan is expressed in midbrain monoaminergic neurons [51]. However, its exact function in dopaminergic signalling is unclear. An *Sgce* knockout murine model demonstrates a striatal hyperdopaminergic state [8] and loss of the epsilon-sarcoglycan protein leads to reduced striatal dopamine D2 receptor binding and enhanced dopamine release [9,52]. In line with this, Luciano et al., showed a response to tetrabenazine in two patients with M-D [53]. At a dose of 75 mg/day, both patients showed marked improvement in myoclonus and mild-to-moderate improvement in dystonia, with sustained effect several years. Tetrabenazine, a reversible inhibitor of vesicular monoamine transporter 2, depletes monoamines, including dopamine, from nerve terminals. Pimozide, another dopamine receptor antagonist, with particularly high affinity for the D2 receptor, was shown to be effective in two patients with myoclonic dystonia [54]. This should, however, be used with caution given the risk of tardive dystonia [55].

Conversely, a study of two unrelated M-D patients showed sustained clinical improvement with L-dopa/carbidopa [56]. At doses of 300mg/day, there was a significant improvement in myoclonus in both patients. This is an unexpected finding given that animal models suggest L-dopa therapy might worsen the condition. Nevertheless, a number of other groups have also reported improvements with L-

dopa [57,58] or, at least, no worsening of symptoms [59,60]. It should also be noted that dopa-responsive dystonia can present with a phenotype mimicking M-D [17].

The response of M-D to GPi-DBS further supports the role of striatal signalling in the pathophysiology of the condition. However, ultra-deep sequencing has shown that expression of the brain-specific isoform of *SGCE* is highest in cerebellar Purkinje cells [61]. Neurophysiological and PET imaging studies also suggest that the cerebellum has a central role in this condition [62,63]. Pharmacological or surgical modulation of basal ganglia output may, therefore, manipulate abnormal cerebellar signalling via disynaptic projections between the subthalamic nucleus and the cerebellar cortex or between the striatum and the dentate nucleus [64]. Ultimately, however, the exact role that dopamine plays in the pathogenesis of M-D is largely unknown and there have been no large case series of tetrabenazine or L-dopa in M-D.

Serotoninergic agents

In addition to elevated levels of striatal dopamine, *Sgce* knockout mice also demonstrate elevated striatal 5-hydroxyindoleacetic acid (5-HIAA, a serotonin metabolite) [8]. Epsilon-sarcoglycan is similarly expressed at a high level in murine serotoninergic neurons [65]. 5-hydroxytryptophan, a precursor of serotonin, has been used historically for treatment of myoclonus, and it has been proposed that myoclonic jerks may be caused by a central serotoninergic deficit resulting in the release of abnormal responses to sensory stimuli [66]. In a large observational study examining several therapies in myoclonic dystonia, 5-hydroxytryptophan was found to be the only effective therapy (although only in two patients and was poorly tolerated by a larger number as high doses are required) [67]. The medication should be co-prescribed with a decarboxylase inhibitor in order to reduce peripheral conversion to serotonin, and hence side effects [68]. In a familial myoclonic dystonia pedigree (not genetically confirmed) there was a significant reduction in myoclonus with 5-hydroxytryptophan [69]. Peall et al. showed low CSF levels of 5-HIAA in four patients with *SGCE* mutations suggesting that there is, indeed, a link between M-D and impaired serotonin homeostasis (rather than simply an association with myoclonus in general) [7]. Interestingly, alcohol has been shown to transiently

increase serotoninergic signalling (as well as activating mesolimbic dopaminergic reward systems) in animal studies, which may provide another mechanism to explain the alcohol-responsiveness seen in M-D [70].

Other medications

Sodium Oxybate, the sodium salt of γ-hydroxybutyrate, a medication licensed for the treatment of cataplexy, improved symptoms by >50% in a small number of M-D patients, as measured by blinded videotape assessment [71,72]. Dose-dependent sedation was the main side effect experienced. The mechanism of action in this setting remains unclear, although it is an effective treatment for alcohol withdrawal and dependence, which is notable in such an alcohol-responsive condition. It may work via the GABA-B receptor either directly or via conversion to its metabolite GABA [71]. Accordingly, the GABA-B agonist baclofen was found to be effective as an anti-myoclonic agent, in particular, for propriospinal spinal myoclonus [73].

Gazzina et al. reported a patient with late-onset M-D, who subsequently developed type 1 diabetes mellitus [74]. The patient reported clear symptom relief following each administration of short-acting insulin. The authors propose that the effect may be mediated via insulin-like growth factor 1 (IGF1) signalling as IGF1 receptors are highly expressed in the cerebellum. There has been recent interest in the role of anti-diabetic agents such as GLP1 receptor antagonists and DPP4 inhibitors in the treatment of Parkinson's disease [75]. Although for some patients the effect may be mainly symptomatic, this finding again suggests converging dopaminergic mechanisms in the pathophysiology of M-D.

Botulinum toxin (BoNT) is the treatment of choice for many focal dystonias [76] and can be useful for focal cases of spinal myoclonus [73]. There have been no clinical trials of BoNT specifically in M-D, however it is likely to be of benefit as in other dystonias and should be considered in the presence of a viable target. In our experience, cervical dystonia in M-D responds well to BoNT and should be considered in addition to treatment of upper limb dystonia.

Deep Brain Stimulation

A detailed discussion of DBS for myoclonic dystonia is beyond the scope of this paper. Initial studies demonstrated efficacy for both GPi-DBS and less commonly ventral intermediate nucleus of the thalamus (VIM) DBS for myoclonus and dystonia in *SGCE*-positive individuals [77–79] and suggested younger age at surgery and shorter disease duration were associated with more favourable outcomes [11]. A number of cases of *SGCE*-negative myoclonic dystonia have responded well to DBS suggesting a benefit for the phenotype, irrespective of underlying genetics [19,20,80]. A recent meta-analysis with individual patient data from 71 patients (51 of whom carried an *SGCE* mutation) confirmed 94.1% showed a >50% improvement in Unified Myoclonus Rating Scale and 79.6% showed a >50% improvement in Burke-Fahn-Marsden Dystonia Rating Scale movement score [81]. There was no difference in efficacy between targets for either outcome. However, pallidal stimulation appears to be associated with fewer adverse stimulation-induced events and most studies have employed GPi-DBS to date [81]. In a small case series, a single patient, in whom bilateral VIM-DBS failed to control progressive dystonia after surgery, benefited from GPI-DBS suggesting that a pallidal target may be more effective for the dystonic component of M-D [82]. In patients stimulated at both sites, the magnitude of improvement appears greater with GPI-DBS [83]. In addition, the motor improvement seen with GPI-DBS appears to be sustained [12] and leads to enhanced quality of life and social adjustment [84]. However, recent studies have raised concern that psychiatric symptoms can worsen following GPi-DBS [85,86]. Hence, similar to medical therapy, motor improvements must be balanced against this potential risk.

Treatment of Psychiatric Comorbidities

The most common psychiatric comorbidities in M-D are anxiety, OCD, depression, phobic disorders and alcohol dependence (with other psychiatric symptoms only reported in single case reports) [5,87]. Whereas motor symptoms tend to remain stable over time, psychiatric symptoms such as depression and anxiety may become more prevalent during the course of the disease [88]. There is a paucity of treatment data specific to M-D in the literature. In our experience, most patients are treated

with monotherapy, most frequently with a selective serotonin reuptake inhibitor (SSRI) with moderate to good effect and good tolerability. Although SSRIs have the potential to worsen myoclonus (particularly at toxic levels), this is not something we have seen in practice in patients with M-D. In addition, there is increasing emphasis on non-pharmacological therapies such as cognitive-behavioral therapy (CBT) for these disorders (OCD and anxiety in particular) which obviates the concern for worsening motor symptoms. The first-line treatment approaches for anxiety, OCD and depression rely heavily on CBT and SSRIs [89–94]. Venlafaxine and other serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, buspirone, gapapentin and ondansetron can be useful in refractory cases as their tolerability is less favourable (e.g. they can worsen myoclonus). By contrast, although second generation antipsychotics, lithium, monoamine oxidase inhibitors, are recommended as third- or fourth-line treatments, they should be used with caution given the possible worsening of dystonia and other higher risk of other side effects. Polytherapy with serotoninergic agents can worsen myoclonus and precipitate serotonin syndrome and risk-benefit of combination therapy should always be weighed. Nevertheless, treatment of debilitating psychiatric comorbidities should not be withheld for this reason. Given the potential for psychiatric symptoms to worsen following GPi-DBS to worsen psychiatric symptoms, neuropsychological assessment is important both before and after surgery [85,86].

Animal Models and Theoretical Frameworks

The role of epsilon sarcoglycan in neuronal physiology is poorly characterised and hence, how *SGCE* mutations give rise to the M-D phenotype is not well understood. Animal models have provided the basis for a number of the treatments outlined above and there have been a number of animal studies which have exposed potential therapeutic targets for M-D.

Maltese et al. demonstrated a striatal plasticity deficit in an *Sgce* knock-out mouse model which is reversed with blockade of adenosine 2A receptors. These receptors modulate the excitability of the medium spiny neurons previously implicated in M-D [95]. This, therefore, implies that adenosine 2A receptor blockade may be of

therapeutic benefit in M-D, as has also been suggested in dystonia caused by *TOR1A* mutations (DYT1) [96].

ADCY5-related disease can present as a myoclonic dystonic syndrome [15]. Functional studies have shown that *ADCY5* mutations increase intracellular cyclic AMP in response to beta agonists [97]. Occasional improvements with propranolol are seen in this condition [98], suggesting that drugs which reduce cAMP may be of benefit in related conditions. However, beta-blockers have not been shown to be of benefit M-D in a small number of trialled cases [31].

Recent studies have also shown the potential benefit of a number of medications in essential tremor (ET), another alcohol-responsive condition. In a similar fashion to M-D, dysfunction of GABAergic projections from the cerebellar cortex have been implicated [99]. In addition, loss of GABA-A receptors in the dentate nucleus (the origin of the cerebellothalamic pathway which may play a role in M-D) occurs highlighting a possible therapeutic target. There is debate over whether phasic inhibition via synaptic GABA-A receptors (activated by benzodiazepines) or tonic inhibition via extrasynaptic GABA-A receptors (predominantly activated by alcohol) is the critical pathogenic mechanism in ET [100]. Recent animal studies have shown that gaboxadol, a highly selective agonist of extrasynaptic GABA-A receptors, is effective at suppressing tremor in a harmaline-induced murine model of ET [101]. A phase 2 trial of allopregnanolone, a progesterone metabolite, which activates both synaptic and extrasynaptic GABA-A receptors is currently underway (Clinicaltrials.gov: NCT02277106). Notably, medications which prolong the duration of opening of GABA-A receptors (such as primidone and benzodiazepines) appear to be more effective in reducing ET but are often limited by side effects [102]. A selective partial agonist of GABA-A, TPA023, which similarly prolongs the duration of opening of the receptor, has been trialled in a small number of alcohol-responsive ET patients, showing a nonsignificant trend towards tremor control compared with placebo [103]. Octanol, a long chain alcohol, and its metabolite octanoic acid, lack the intoxicating effect of ethanol and have been studied as possible alternatives for tremor suppression in ET. Preliminary studies have suggested benefit [104] but it is

likely that very large doses will be required to be effective, and studies involving larger cohorts are needed. Given the possible pathophysiological similarities and alcohol responsiveness seen in both conditions, new medications which prove effective in the management of ET may guide future trials in M-D. A summary of the mechanisms of action of the most important medications which have been trialled in the myoclonic dystonias and M-D is shown in Table 1.

Discussion

M-D is a complex disorder with many different facets, and for which there remains a paucity of data on specific medical therapies. GPi-DBS has been shown to be an effective symptomatic treatment with sustained benefit. However, there is a cohort of patients who are not eligible for surgery, either due to severity of psychiatric comorbidity, other comorbidities or whose symptoms are deemed not severe enough to warrant surgery. Other patients may decline surgery. For these groups, effective monotherapy, or combinations of medical therapy are critical to their quality of life. Only a single randomized controlled trial for medical treatment of M-D has been undertaken to date with some beneficial effect. Evidence for other medical therapies is limited and also conflicting (e.g. improvement with either tetrabenazine or L-dopa). For this reason, treatment decisions are largely ad hoc, and results are essentially limited by the tolerability of the medication and genetic heterogeneity of the myoclonic dystonias. Unpredictable response to treatment in individual patients is further complicated by unpredictable side effects. Treatment goals are, therefore, to improve a particular facet or facets of the disorder (myoclonus, dystonia, psychiatric symptoms), while balancing the potential for that medication to worsen other facets of the disorder (in particular myoclonus or psychiatric symptoms). We propose an algorithm to help guide the medical treatment of M-D below (Figure 1).

Given the variability of responses in individual patients, the overall approach will, however remain pragmatic and empirical rather than prescriptive. In general, monotherapy is advised in the first instance to minimise side effects and determine response. The initial choice of medication will depend on the severity of motor symptoms. For example, a patient with mild myoclonus may respond to a generic

anti-myoclonic agent such as clonazepam, whereas for more prominent myoclonus, an anticonvulsant may be required (with caution regarding psychiatric comorbidity) with a low threshold to add clonazepam if response is suboptimal. A patient with severe myoclonus may ultimately require two anticonvulsants in addition to clonazepam in order to obtain benefit. If the predominant symptom is dystonia, on the other hand, depending on distribution, botulinum toxin would be first line for cervical dystonia +/- forearm muscles in adults. Trihexyphenidyl is the most frequently employed medication for dystonia in adults and children with generally good efficacy and overall good safety profile at low doses. Slow titration is always advised, observing for efficacy and the emergence of side effects. It should be noted, however, that if a patient is severely affected, GPI-DBS is likely to be the most effective treatment. If the patient is a good surgical candidate and a few first and second line agents are ineffective, an expeditious route to surgery should be undertaken rather than exhausting all available medical options first.

The precise pathophysiological pathways of this disorder remain elusive. A detailed review of the current literature on pathogenesis is given in Roze et al [10]. Dysfunction of cerebellothalamic networks (possibly via a GABAergic deficit of Purkinje cells) may be the dominant pathomechanism, explaining the established use of medications which enhance GABAergic transmission. Neuroimaging studies point to the parasagittal cerebellum and brainstem [62,105], while neurophysiological studies demonstrate abnormal neuronal activity in the GPi [106,107]. Debate remains whether striato-pallido-thalamo-cortical pathways are the primary networks involved in M-D (explaining the exquisite response of the disorder to GPi-DBS) or whether cerebellothalamic pathways are the main culprit (a hypothesis supported by functional imaging [62], molecular [61], and neurophysiological [63] studies implicating cerebellar dysfunction). A recent murine study demonstrated that the motor features of M-D could be reproduced via acute knockdown of *sgce* in the cerebellum but not in the basal ganglia, providing further support for a primarily cerebellothalamic pathophysiology [108]. The expression of $GABA_A$ receptors and T-type calcium channels (the target of zonisamide) throughout both pathways provides an attractive explanation for the effect of zonisamide in this condition. In addition,

there is some evidence of abnormalities in serotoninergic and dopaminergic homeostasis in M-D. Low levels of CSF serotonin metabolites [7] and reduced dopamine D2 receptor availability [9] in patients with M-D suggest that alteration in monoaminergic signalling may be central to the condition, as well as providing a possible therapeutic target. Medications shown to be effective in M-D and myoclonic dystonias are shown in Figure 2, along with possible primary sites of action.

As mentioned above, myoclonic dystonias are a genetically heterogeneous group of disorders and it has been suggested that networks of genes may be involved in the pathogenesis of many dystonias. In this way, multiple physiological pathways may be implicated in myoclonic dystonias. Genes involved in calcium homeostasis (*ANO3* [16], *KCTD17* [109]), dopaminergic signalling (*TH* [23], *GCH1* [17]) and other pathways have all been shown to cause myoclonic dystonia. Future therapies may therefore target networks of genes and pathways rather than focusing on a single gene (e.g. *SGCE*). The expanding spectrum of genes which can cause a myoclonic dystonia syndrome has been recently reviewed [14].

Ultimately, response to treatment will lead to important insights into the dominant underlying pathogenic mechanisms in M-D. Animal models may provide a theoretical framework for future therapies but they have also generated findings inconsistent with what observed in human patients. Aside from basic science research, large controlled studies are required in genetically well-defined cohorts of patients to further validate the therapeutic options based on either translational research or serendipity.

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Figure Legends:

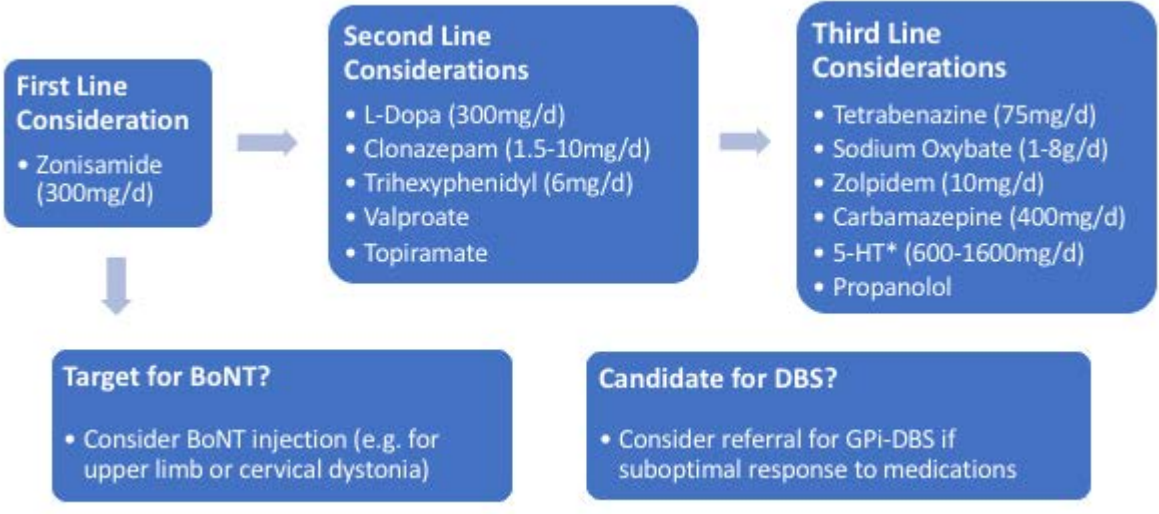
Figure 1. Flowchart of treatment considerations in myoclonus-dystonia. Associated doses are given (if published). *Co-prescribe with a decarboxylase inhibitor.

Figure 2. Medications effective in myoclonus-dystonia and myoclonic dystonias and possible sites of action. The sites of action of a number of other medications are unknown and may be widespread (e.g. valproate, topiramate, sodium oxybate). Many medications may act at multiple sites and thus, only the proposed dominant site of action is shown. 5-HT = serotonin; Ach = acetylcholine; DA = dopamine; GPi = globus pallidus interna. Modified from Morgante & Klein [110], with permission.

Table 1. Mechanisms of action of the drugs trialled in M-D and myoclonic dystonias.

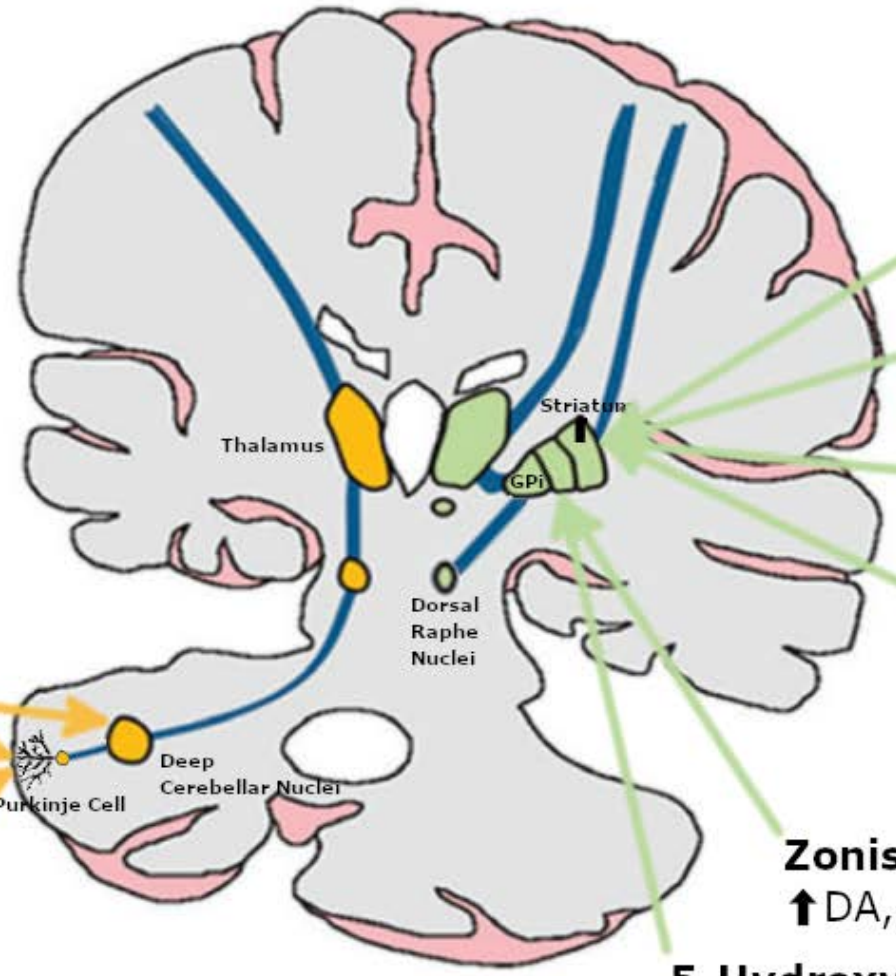
Drug	Tested in		Mechanism of action				Note	Reference(s)
	M-D	Myoclonic-dystonia(s)	DA	GABA	5-HT	Other		
Zonisamide	+	-	+/-	+/-	+/-	Inhibition of T-type calcium channels	Only RCT available so far	Hainque et al. [28]
Valproate	+	+		+/-		Inhibition of voltage-gated Na channels	Anti-myoclonic effect	Thümmler et al. [35]
Topiramate	-	+		+/-		Multiple mechanisms of action	Anti-myoclonic effect	Raymond & Ozelius.[36]
Carbamazepine	+	-	+/-		+/-	Inhibition of voltage-gated Na channels		Moghaddam et al.[38]
Clonazepam	-	+		+			Most likely effect on cerebellar Purkinje cells	Obeso et al[2].; Kinugawa et al.[4]
Zolpidem	-	+		+			Highest expression in GPi, SNr, STN	Park et al. [46]
Trihexyphenidyl	+	+	+/-			Unclear MOA	May restore imbalance between striatal DA and ACh	Lee et al. [49]
Tetrabenazine	+	-	+				Depletes monoamines	Luciano et al.[53]
Levodopa	+	+	+					Luciano et al.[56]
5-hydroxytryptophan	-	+	+/-		+		Co-prescribe with a decarboxylase inhibitor	Przuntek & Muhr.[67]
Sodium Oxybate	+	-		+			Caution re: sedation	Frucht et al.[71] ; Priori et al.[72]
Propanolol	-	+				Reduces cAMP	Evidence in ADCY5	Chang et al.[80]

Abbreviations: 5-HT = serotonin; Ach = acetylcholine; ADCY5 = Adenylate Cyclase 5; cAMP = Cyclic adenosine monophosphate; DA = dopamine; GPi = globus pallidus interna; SNr = substantia nigra pars reticularis; STN = subthalamic nucleus.


First Line Consideration
• Zonisamide (300mg/d)
Second Line Considerations
• L-Dopa (300mg/d)
• Clonazepam (1.5-10mg/d)
• Trihexyphenidyl (6mg/d)
• Valproate
• Topiramate
Third Line Considerations
• Tetrabenazine (75mg/d)
• Sodium Oxybate (1-8g/d)
• Zolpidem (10mg/d)
• Carbamazepine (400mg/d)
• 5-HT* (600-1600mg/d)
• Propanolol
Target for BoNT?
• Consider BoNT injection (e.g. for upper limb or cervical dystonia)
Candidate for DBS?
• Consider referral for GPi-DBS if suboptimal response to medications

Cerebello-thalamo-cortical network

Striato-pallido-thalamo-cortical network



Zonisamide
?⬆GABA

Benzodiazepines
⬆GABA

Levodopa
⬆ DA

Tetrabenazine
⬇DA, ⬇5-HT

Carbamazepine
⬆DA, ⬆5-HT

Zolpidem
⬆GABA

Trihexyphenidyl
⬇ACh, ?⬆DA

Zonisamide
⬆DA, ⬆5-HT

5-Hydroxytryptophan
⬆5-HT