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## **Medical Management of Myoclonus-Dystonia and Implications for Underlying Pathophysiology**

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**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.

## 1 Introduction

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

13

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

22

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

31

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

20

## 21 **Zonisamide**

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

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

13

#### 14 **Other antiepileptic medications**

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

23

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

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

11

### 12 **Benzodiazepines**

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

22

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

31

### 32 **Anticholinergic agents**

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

10

### 11 **Dopaminergic agents**

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

26

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



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

3

4 The response of M-D to GPi-DBS further supports the role of striatal signalling in the  
5 pathophysiology of the condition. However, ultra-deep sequencing has shown that  
6 expression of the brain-specific isoform of *SGCE* is highest in cerebellar Purkinje cells  
7 [61]. Neurophysiological and PET imaging studies also suggest that the cerebellum  
8 has a central role in this condition [62,63]. Pharmacological or surgical modulation of  
9 basal ganglia output may, therefore, manipulate abnormal cerebellar signalling via  
10 disynaptic projections between the subthalamic nucleus and the cerebellar cortex or  
11 between the striatum and the dentate nucleus [64]. Ultimately, however, the exact  
12 role that dopamine plays in the pathogenesis of M-D is largely unknown and there  
13 have been no large case series of tetrabenazine or L-dopa in M-D.

14

#### 15 **Serotonergic agents**

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

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

4

#### 5 **Other medications**

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

15

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

25

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

32

## 1 **Deep Brain Stimulation**

2 A detailed discussion of DBS for myoclonic dystonia is beyond the scope of this  
3 paper. Initial studies demonstrated efficacy for both GPI-DBS and less commonly  
4 ventral intermediate nucleus of the thalamus (VIM) DBS for myoclonus and dystonia  
5 in *SGCE*-positive individuals [77–79] and suggested younger age at surgery and  
6 shorter disease duration were associated with more favourable outcomes [11]. A  
7 number of cases of *SGCE*-negative myoclonic dystonia have responded well to DBS  
8 suggesting a benefit for the phenotype, irrespective of underlying genetics  
9 [19,20,80]. A recent meta-analysis with individual patient data from 71 patients (51  
10 of whom carried an *SGCE* mutation) confirmed 94.1% showed a >50% improvement  
11 in Unified Myoclonus Rating Scale and 79.6% showed a >50% improvement in Burke-  
12 Fahn-Marsden Dystonia Rating Scale movement score [81]. There was no difference  
13 in efficacy between targets for either outcome. However, pallidal stimulation  
14 appears to be associated with fewer adverse stimulation-induced events and most  
15 studies have employed GPI-DBS to date [81]. In a small case series, a single patient,  
16 in whom bilateral VIM-DBS failed to control progressive dystonia after surgery,  
17 benefited from GPI-DBS suggesting that a pallidal target may be more effective for  
18 the dystonic component of M-D [82]. In patients stimulated at both sites, the  
19 magnitude of improvement appears greater with GPI-DBS [83]. In addition, the  
20 motor improvement seen with GPI-DBS appears to be sustained [12] and leads to  
21 enhanced quality of life and social adjustment [84]. However, recent studies have  
22 raised concern that psychiatric symptoms can worsen following GPI-DBS [85,86].  
23 Hence, similar to medical therapy, motor improvements must be balanced against  
24 this potential risk.

25

## 26 **Treatment of Psychiatric Comorbidities**

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

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

21

## 22 **Animal Models and Theoretical Frameworks**

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

28

29 Maltese et al. demonstrated a striatal plasticity deficit in an *Sgce* knock-out mouse  
30 model which is reversed with blockade of adenosine 2A receptors. These receptors  
31 modulate the excitability of the medium spiny neurons previously implicated in M-D  
32 [95]. This, therefore, implies that adenosine 2A receptor blockade may be of

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

3

4 *ADCY5*-related disease can present as a myoclonic dystonic syndrome [15].

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

10

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

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

7

## 8 **Discussion**

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

27

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

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

15

16 The precise pathophysiological pathways of this disorder remain elusive. A detailed  
17 review of the current literature on pathogenesis is given in Roze et al [10].

18 Dysfunction of cerebellothalamic networks (possibly via a GABAergic deficit of  
19 Purkinje cells) may be the dominant pathomechanism, explaining the established use  
20 of medications which enhance GABAergic transmission. Neuroimaging studies point  
21 to the parasagittal cerebellum and brainstem [62,105], while neurophysiological  
22 studies demonstrate abnormal neuronal activity in the GPi [106,107]. Debate  
23 remains whether striato-pallido-thalamo-cortical pathways are the primary networks  
24 involved in M-D (explaining the exquisite response of the disorder to GPI-DBS) or  
25 whether cerebellothalamic pathways are the main culprit (a hypothesis supported by  
26 functional imaging [62], molecular [61], and neurophysiological [63] studies  
27 implicating cerebellar dysfunction). A recent murine study demonstrated that the  
28 motor features of M-D could be reproduced via acute knockdown of *sgce* in the  
29 cerebellum but not in the basal ganglia, providing further support for a primarily  
30 cerebellothalamic pathophysiology [108]. The expression of GABA<sub>A</sub> receptors and T-  
31 type calcium channels (the target of zonisamide) throughout both pathways provides  
32 an attractive explanation for the effect of zonisamide in this condition. In addition,

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

7

8 As mentioned above, myoclonic dystonias are a genetically heterogeneous group of  
9 disorders and it has been suggested that networks of genes may be involved in the  
10 pathogenesis of many dystonias. In this way, multiple physiological pathways may be  
11 implicated in myoclonic dystonias. Genes involved in calcium homeostasis (*ANO3*  
12 [16], *KCTD17* [109]), dopaminergic signalling (*TH* [23], *GCH1* [17]) and other  
13 pathways have all been shown to cause myoclonic dystonia. Future therapies may  
14 therefore target networks of genes and pathways rather than focusing on a single  
15 gene (e.g. *SGCE*). The expanding spectrum of genes which can cause a myoclonic  
16 dystonia syndrome has been recently reviewed [14].

17

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

25

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28

## 29 **Documentation of Author Roles**

- 30 1) Research project: A. Conception, B. Organization, C. Execution;  
31 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;  
32 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

33

34 CF 1B, 1C, 3A



1 KP 3B  
 2 MV 3B  
 3 AF 1A, 1B, 3B

4

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8 KP

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1

2

AF

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1 **Figure Legends:**

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

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6 **Figure 2.** Medications effective in myoclonus-dystonia and myoclonic dystonias and  
7 possible sites of action. The sites of action of a number of other medications are  
8 unknown and may be widespread (e.g. valproate, topiramate, sodium oxybate).

9 Many medications may act at multiple sites and thus, only the proposed dominant  
10 site of action is shown. 5-HT = serotonin; Ach = acetylcholine; DA = dopamine; GPi =  
11 globus pallidus interna. Modified from Morgante & Klein [110], with permission.

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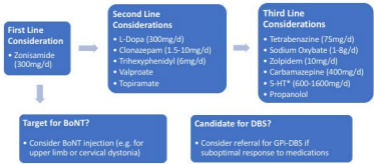
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**Table 1.** Mechanisms of action of the drugs trialled in M-D and myoclonic dystonias.

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. <sup>28</sup>
Valproate	+	+		+/-		Inhibition of voltage-gated Na channels	Anti-myoclonic effect	Thümmeler et al. <sup>35</sup>
Topiramate	-	+		+/-		Multiple mechanisms of action	Anti-myoclonic effect	Raymond & Ozelius. <sup>36</sup>
Carbamazepine	+	-	+/-		+/-	Inhibition of voltage-gated Na channels		Moghaddam et al. <sup>38</sup>
Clonazepam	-	+		+			Most likely effect on cerebellar Purkinje cells	Obeso et al. <sup>2</sup> ; Kinugawa et al. <sup>4</sup>
Zolpidem	-	+		+			Highest expression in GPi, SNr, STN	Park et al. <sup>46</sup>
Trihexyphenidyl	+	+	+/-			Unclear MOA	May restore imbalance between striatal DA and ACh	Lee et al. <sup>49</sup>
Tetrabenazine	+	-	+				Depletes monoamines	Luciano et al. <sup>53</sup>
Levodopa	+	+	+					Luciano et al. <sup>56</sup>
5-hydroxytryptophan	-	+	+/-		+		Co-prescribe with a decarboxylase inhibitor	Przuntek & Muhr. <sup>67</sup>
Sodium Oxybate	+	-		+			Caution re: sedation	Frucht et al. <sup>71</sup> ; Priori et al. <sup>72</sup>
Propranolol	-	+				Reduces cAMP	Evidence in ADCY5	Chang et al. <sup>80</sup>

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.



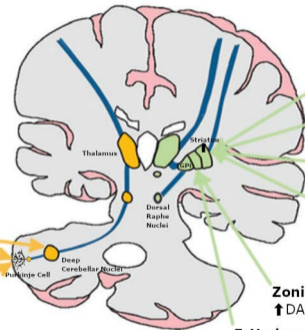


**Cerebello-thalamo-cortical network**

**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