Dystonia: Phenomenology and diagnosis, Classification, Genetics and Pathophysiology

Cynthia L. Comella, MD
Oppenheim coined the term “dystonia musculorum deformans” in 1911.

- muscle spasms, bizarre gait (dromedary) and progressive nature

Until 1970’s, considered “hysterical” despite accumulating evidence to the contrary

- Felt to be organic disease
  - Ernst Herz, 1944
- Recognized the autosomal dominant pattern of inheritance
  - Zemen, 1959
- Limited benefit of psychotherapy
  - Eldridge, 1969
- Animal model with basal ganglia lesion
  - Denny-Brown, 1965
A History of Dystonia: Ancient to Modern

Rachel E. Newby, MA, MB, BCHr, MRCP (UK),1,2,3 Deborah E. Thorpe, MSc, PhD,4,5 Peter A. Kempster, MB, BS, MD, MRCP (UK), FRACGP1,2
June E. Aliy, MA, MB, BCHr, MD, MRCP (UK)1,2,5

Abstract: Before 1911, when Hermann Oppenheim introduced the term dystonia, this movement disorder lacked a unifying descriptor. While words like epilepsy, apoplexy, and palsy have had their meanings since antiquity, references to dystonia are much harder to identify in historical documents. Torticollis is an exception, although there is difficulty distinguishing dystonic torticollis from congenital muscular torticollis. There are, nevertheless, possible representations of dystonia in literature and visual art from the pre-modern world. Eighteenth century systematic nosologists such as Linnaeus, de Sauvages, and Cullen had attempted to classify some spasmodic conditions, including torticollis. But only after Charcot’s contributions to clinical neuroscience were the various forms of generalized and focal dystonia clearly delineated. They were categorized as návroses: Charcot’s term for conditions without an identifiable neuroanatomical cause. For a time thereafter, psychoanalytic models of dystonia based on Freud’s ideas about unconscious conflicts transduced into physical symptoms were ascendant, although there was always a dissenting “organic” school. With the rise of subspecialization in movement disorders during the 1970s, the pendulum swung strongly back toward organic causation. David Marsden’s clinical and electrophysiological research on the adult-onset focal dystonias was particularly important in establishing a physical basis for these disorders. We are still in a period of “living history” of dystonia, with much yet to be understood about pathophysiology. Rigidly dualistic models have crumbled in the face of evidence of electrophysiological and psychopathological overlap between organic and functional dystonia. More flexible biopsychosocial frameworks may address the demand for new diagnostic and therapeutic rationales.
First consensus definition:

*Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures*

Camargo et al. Arq Neuropsiquiatr 2014

Fahn S. Adv Neurol 1988;50:1-8
“Hysterical” or neurological?
Topics

- Phenomenology and diagnosis
- Classification
- Genetics
- Pathophysiology
Dystonia: Phenomenology

- A syndrome, not a disease
- Involuntary, relatively sustained muscle contractions
- Usually producing twisting and repetitive movements or abnormal postures
- Remissions infrequent and often recurrence

Jinnah HA. The Dystonias. Continuum (Minneap Minn). 2019
Mainka T et al Remission in dystonia – Parkinsonism Relat Disord. 2019
Dystonia Phenomenology

- Varies with changes in posture or activity
- Triggered or increased by voluntary action
  - Writer’s cramp, musician dystonia

Albanese A, Di Giovanni M, Lalli S. Eur J Neurol. 2019
Dystonia Phenomenology

- Sensory “tricks”
  - geste antagonist, alleviating maneuver
    - Tactile or proprioceptive maneuvers that improve dystonia
    - Imagining sensory trick may also be effective

Patel N et al. J Neurol Neurosurg Psychiatry 2014
Dystonia: Suggested diagnostic criteria

Italian Movement Disorder Experts

Methods
Panel of 4 neurologists
List of clinical items related to dystonia
10 additional expert neurologists assessed relevance of selected features
Content validity ratio calculated
If CVR > 0.5 lead to final recommendations

- **Diagnosis CD**
  - Patterned and repetitive head/neck postures
  - Spontaneous or triggered by motor tasks
  - Head deviation from neutral
  - With or without tremor
  - Presence of a sensory trick

- **Limb dystonia**
  - Patterned and repetitive movements
  - Spontaneous or triggered by motor tasks
  - One or more segments of upper/lower extremity
  - With or without tremor
  - Presence of a sensory trick

Defazio et al. Neurological Sciences 2019
Dystonia Crude Prevalence

- Generalized dystonia
  - Prevalence between 4-50 per million

- Focal dystonia
  - Prevalence between 61 - 329 per million
    - Approximately 10 times more frequent than generalized dystonia
    - Cervical most frequent in clinic practice
    - Writer’s cramp thought to be most common in community

- In 944 patients in Kaiser Permanente system, cervical dystonia incidence 1.18/100,000 person years, increased with age, greater in women, diagnostic delay of median 2 years, delaying treatment

LaHue et al. Move Disord 2019
Topics

- Phenomenology and diagnosis
- Classification
- Genetics
- Pathophysiology
# Classification of dystonia

**1. By age at onset**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>A.</td>
<td>Early-onset: ≤ 26 years</td>
</tr>
<tr>
<td>B.</td>
<td>Late-onset: &gt; 26 years</td>
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**2. By distribution**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A.</td>
<td>Focal</td>
</tr>
<tr>
<td>B.</td>
<td>Segmental</td>
</tr>
<tr>
<td>C.</td>
<td>Multifocal</td>
</tr>
<tr>
<td>D.</td>
<td>Generalized</td>
</tr>
<tr>
<td>E.</td>
<td>Hemidystonia</td>
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</tbody>
</table>

**3. By etiology**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A.</td>
<td>Primary (also known as idiopathic) dystonia</td>
</tr>
<tr>
<td>B.</td>
<td>Dystonia -plus</td>
</tr>
<tr>
<td>C.</td>
<td>Secondary dystonia (environmental insult)</td>
</tr>
<tr>
<td>D.</td>
<td>Here, degenerative dystonia (usually presents as dystonia -plus)</td>
</tr>
<tr>
<td>E.</td>
<td>A feature of another neurologic disease (e.g., dystonic tics, paroxysmal dyskinesias, PD, progressive supranuclear palsy)</td>
</tr>
</tbody>
</table>

Revised definition and classification of Dystonia

- Consensus Committee:
  - The Dystonia Medical Research Foundation, the Dystonia Coalition and the European Dystonia Cooperation in Science and Technology organized a to propose a modification of the classification scheme for dystonia.

- The revised definition of dystonia:
  - Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned, twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese et al. Move Disord 2013
Revised Classification

- **Axis I: Clinical characteristics**
  - Age at onset
  - Body Distribution
  - Temporal pattern

- **Axis II: Etiology**
  - Nervous system pathology
  - Inherited or acquired

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**Phenomenology and classification of dystonia: A consensus update**

Alberto Albanese MD, Kailash Bhatia MD, FRCP, Susan B. Bressman MD, Mahlon R. DeLong MD, Stanley Fahn MD, Victor S.C. Fung PhD, FRACP, Mark Hallett MD. ... See all authors

First published: 06 May 2013 | https://doi.org/10.1002/mds.25475 | Cited by: 470

Relevant conflicts of interest/financial disclosures: Full financial disclosures and author roles may be found in the Acknowledgments section online.
Axis I: Clinical Characteristics

- **Age of onset**
  - **Infancy** (birth to 2 years)
    - Example: High probability of being metabolic disease
  - **Childhood** (3-12 years)
    - Example: Cerebral palsy, DRD
  - **Adolescence** (13-20 years)
    - Genetic causes
  - **Early adulthood** (21-40)
  - **Late adulthood** (>40)
    - Sporadic focal dystonia

Albanese et al. Move Disord 2013
Axis I: Body distribution

- **Focal**: one body region (eyes, facial, neck, limb, trunk)
- **Segmental**: 2 or more contiguous body areas (craniofacial dystonia)
- **Multifocal**: 2 or more non contiguous body areas
- **Generalized**: trunk and at least 2 other body areas
- **Hemidystonia**: restricted to one body side
Primary Dystonia: Age of Onset and Area of Onset

Primary Dystonia: prognosis for spread of dystonia

Axis I: Temporal Pattern

- Persistent
- Action specific
- Diurnal fluctuations
- Paroxysmal

Albanese et al. Move Disord 2013
Temporal Pattern: Diurnal variation
Dopa-responsive dystonia

- Dystonia and parkinsonism
- Onset in childhood (may be misdiagnosed as CP)
- Autosomal dominant (GCH1 mutation)
- GTP cyclohydrolase 1
  - rate limiting step for tetrahydrobiopterin
- Sustained response to low dose levodopa without motor complications in most

Jinnah HA, Sun YV. Neurobiology of Disease 2019
Dystonia: Classification

Axis 2: Etiology

- Inherited or Acquired
  - Inherited
  - Acquired
  - Idiopathic: sporadic or familial

- Nervous system pathology
  - Degeneration (progressive structural abnormality)
  - Static (non-progressive neurodevelopmental or acquired lesions)
  - No evidence of degeneration or structural lesion

Albanese et al. Move Disord 2013
Axis 2: Inherited

- Autosomal dominant
- Autosomal Recessive
- X-linked recessive
- Mitochondrial
Axis 2 Inherited etiology

Axis I
Onset: childhood
Body distribution: Generalized
Temporal pattern: Progressive without variation
Associated features: Combined with myoclonus

Axis II
Inherited, autosomal dominant

MYOCLONUS DYSTONIA (DYT11)

Mother, maternal grandmother, brother and sister affected
Axis 2: Acquired etiology

- Dystonia due to a specific cause
  - Perinatal brain injury (dystonic CP)
  - Infection
  - Drugs
  - Toxic
  - Vascular
  - Neoplastic
  - Brain injury
  - Functional

- Tardive dystonia

- SSPE
Axis 2: Acquired etiology

Functional (psychogenic) dystonia
Axis 2: Nervous system pathology

- Degeneration (progressive structural abnormality)
- Static lesions (non progressive neurodevelopmental anomalies or acquired lesions)
- No evidence of degeneration or structural lesion

Albanese et al. Move Disord 2013
Axis 2: Degenerative

Neurogeneration with Bran Iron Accumulation: Pantothenate Kinase Associated Neurodegeneration Type 2 (PANK2)

Jinnah HA, Sun YV. Neurobiology of Disease 2019
Axis 2: Static Lesions

- Axial CT scan of the neck demonstrates atlantoaxial rotary subluxation at C1-C2.
How well does the new classification system work?

- Pilot study involving independent classification of 56 cases of dystonia by 8 movement disorder specialists
  - Only 16.1% had 100% agreement for all Axis I (clinical characteristics) items
    - Van Egmond et al. Move Disord 2019

- Literature search for use of new vs old classification
  - 990 articles identified
    - 59.8% used the classification correctly
    - 31.3% used mixed terminology
    - 8.9% used the old classification
    - Use of new classification on the increase since publication in 2013-2018
      - Sasikumar S et al. Move Disord Clin Practice 2019
“Harmonized, specific and internationally used classifications provide the basis for future systematic dystonia research”

Grutz K, Klein C. J Neural Trans 2021
Topics

- Phenomenology and diagnosis
- Classification
- Genetics
- Pathophysiology
Genetics

- Isolated dystonia
  - Dystonia only motor feature with exception of tremor

- Combined dystonia:
  - Dystonia combined with other movement disorders
### Isolated Dystonia Genetics

<table>
<thead>
<tr>
<th>Classification</th>
<th>Chromosome Gene mutation</th>
<th>Pattern of inheritance</th>
<th>Onset</th>
<th>Distribution, additional features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1-TOR1A</td>
<td>9q34, GAG deletion, missense mutations, TOR1A/TorsinA</td>
<td>AD</td>
<td>C</td>
<td>Distal limbs, generalized Penetrance: 30% AJ, 70% NJ</td>
</tr>
<tr>
<td>DYT2</td>
<td>1p35.1 HPCA/hippocalcin</td>
<td>AR</td>
<td>C</td>
<td>Upper limbs, cranial-cervical, generalized, Spanish gypsies, Sephardic Jews</td>
</tr>
<tr>
<td>DYT6-THAP1</td>
<td>8q21-22 THAP1</td>
<td>AD</td>
<td>A,C</td>
<td>Cervical, cranial, brachial German-American Mennonite-Amish</td>
</tr>
<tr>
<td>DYT7</td>
<td>18p</td>
<td>AD</td>
<td>A</td>
<td>Cervical, cranial, spasmodic dysphonia, hand tremor</td>
</tr>
<tr>
<td>DYT13</td>
<td>1p36.13-32</td>
<td>AD</td>
<td>A,C</td>
<td>Cranial-cervical and upper limb</td>
</tr>
<tr>
<td>DYT17</td>
<td>20p11.22-q13.12</td>
<td>AR</td>
<td>C</td>
<td>Cervical dystonia, dysphonia, segmental, generalized</td>
</tr>
<tr>
<td>DYT21</td>
<td>2q14.3-q21.3</td>
<td>AD</td>
<td>A</td>
<td>Late-onset</td>
</tr>
<tr>
<td>DYT23</td>
<td>9q34.11, CIZ1</td>
<td>AD</td>
<td>A</td>
<td>Cervical</td>
</tr>
<tr>
<td>DYT24-ANO3</td>
<td>3, AMO3</td>
<td>AD</td>
<td>C,A</td>
<td>Cranial-cervical-laryngeal, tremor, myoclonus</td>
</tr>
<tr>
<td>DYT25-GNAL</td>
<td>18p, GNAL</td>
<td>AD</td>
<td>A</td>
<td>Cervical&gt;cranial&gt;arm &gt;laryngeal</td>
</tr>
<tr>
<td>DYT27</td>
<td>2q37.3 ATP1A2, COL6A3</td>
<td>AR</td>
<td>C,A</td>
<td>Cranial-cervical, upper limbs, and trunk</td>
</tr>
</tbody>
</table>

Jinnah HA, Sun YV Neurobiol Dis. 2019
DYT1 Dystonia

- Childhood onset
- Generalized
- Isolated dystonia
- No evidence of degeneration
- Inherited

Bressman et al. Neurology 2000;54:1746-52
DYT1 (TOR1A) Dystonia

- **Disease Frequency:**
  - 1/3000-1/9,000 in Ashkenazi Jews
  - 1/9,000-1/27,000 in non-Jews

- **Age-Onset:**
  - Average of 13 yrs (3-44)

- **Phenotype:**
  - Onset limb (>90%)
  - >50% generalize
  - Spares craniocervical region

- **Inheritance:**
  - autosomal dominant
  - \(\approx 30\%\) penetrance

- **Mutation**
  - GAG deletion, chr 9q34

- **Protein:**
  - TorsinA

Testing for DYT1 available. Test only for onset < 26 years or in older if family history of young onset dystonia

Bressman et al. Neurology 2000;54:1746-52
Domingo A, Yadav R, Ozelius L. J Neural Trans 2021
THAP1: Adolescent onset, generalized with prominent orofacial involvement, 60% penetrant
<table>
<thead>
<tr>
<th>Classification</th>
<th>Chromosome Gene mutation</th>
<th>Pattern of inheritance</th>
<th>Onset</th>
<th>Distribution, additional features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT3-PARK-TAF1</td>
<td>Xq TAF1</td>
<td>XR</td>
<td>A</td>
<td>Parkinsonism Filipino (Lubag) mosaic striatal gliosis</td>
</tr>
<tr>
<td>DYT4-TUBB4A</td>
<td>19p13.3-p13.2 TUBB4 (β-tubulin 4a)</td>
<td>AD</td>
<td>C,A</td>
<td>Whispering dysphonia, cranial, cervical, limb, hobby horse gait disorder, facial atrophy, ptosis, edentulous</td>
</tr>
<tr>
<td>DYT5c-PARK-GCH1</td>
<td>1q42.1 GCH1/GTP cyclohydrolase I</td>
<td>AD</td>
<td>C</td>
<td>Dopa-responsive dystonia, diurnal fluctuation, gait disorder, parkinsonism, myoclonus, spasticity</td>
</tr>
<tr>
<td>DYT5b-PARK-TH</td>
<td>11p15.5 tyrosine hydroxylase</td>
<td>AR</td>
<td>C</td>
<td>Dopa-responsive dystonia, gait disorder, parkinsonism, myoclonus, spasticity</td>
</tr>
<tr>
<td>DYT11-SGCE</td>
<td>7q21.3 SGCE Epsilon-sarcoglycan</td>
<td>AD</td>
<td>C</td>
<td>Myoclonus-dystonia, alcohol-responsive, OCD, drug addiction</td>
</tr>
<tr>
<td>DYT12-PARK-ATP1A3</td>
<td>19q13.2 ATP1A3 Na+/K+ ATPase</td>
<td>AD</td>
<td>C,A</td>
<td>Rapid-onset-dystonia-parkinsonism, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome, (CAPOS), alternating hemiplegia of childhood</td>
</tr>
<tr>
<td>DYT15</td>
<td>18p11</td>
<td>AD</td>
<td>C</td>
<td>Myoclonus-dystonia</td>
</tr>
<tr>
<td>DYT16-PRKRA</td>
<td>2q31.2 PRKRA</td>
<td>AD</td>
<td>C</td>
<td>Predominately lower limb, axial, oromandibular, and laryngeal dystonia, parkinsonism, unresponsive to levodopa</td>
</tr>
<tr>
<td>DYT26</td>
<td>22q12 KCTD17</td>
<td>AD</td>
<td>C,A</td>
<td>Myoclonus-dystonia Cranial-cervical</td>
</tr>
</tbody>
</table>

Jinnah HA, Sun YV Neurobiol Dis. 2019
Combined dystonias

- XDP, Lubag, DYT3-TAF1
- Filipinos
- Panay Islands, Philippines
- X linked recessive
- Adult onset
- Progressive dystonia and parkinsonism, mortality at mean 55y
- Mosaic strital gliosis
- May improve with DBS

Kawari et al. Brain Sciences 2017
Tisch S, Kumar KR. Front Neurol 2021
Topics

- Phenomenology and diagnosis
- Classification
- Genetics
- Pathophysiology
Pathophysiology of dystonia

- Defect in sensory function and sensorimotor integration
  - Spatial and temporal domains

- Maladaptive plasticity
  - Somatosensory cortex with larger receptive fields and overlapping representation (digits in hand dystonia)

- Loss of surround inhibition
  - Overactive direct pathway, underactive indirect pathway

Jinnah HA, Hess E. Parkinsonism Rel Disord 2018
Pathophysiology of dystonia

- Network disorder
  - Abnormal functioning of involved node(s)
    - Basal ganglia, cerebellum, brain stem, thalamus, cortex

Prudente, Hess, Jinnah. Neuroscience 2014
Neychev et al, Neurobiol Dis 2011
The Basal Ganglia
Function of the basal ganglia

- Finesse the cortical network involved in motor performance
- Reinforce learning and memorization of behavioral routines
  - Sequences of action, nearly automatic
  - Performed without thinking
- Writing, knitting, playing a musical instrument, riding a bicycle

Ribot B et al. Progress in Neurobiol 2019
Center-surround inhibition

Balance of cholinergic and dopaminergic modulation underlies control of motor function in the basal ganglia

Acetylcholine has powerful influence on striatal dopamine neurotransmission and modulates MSN in basal ganglia
  - Critical role in plasticity and motor learning

Imbalanced cholinergic transmission and effects on DA receptors suggested to be pivotal in DYT1 dystonia
  - Increased cholinergic interneuron activity

Jaunaraiks et al. Prog Neurobiol 2016
Research Paper

Strength of cholinergic tone dictates the polarity of dopamine D2 receptor modulation of striatal cholinergic interneuron excitability in DYT1 dystonia

Mariangela Scarduzio a,1, Chelsea N. Zimmerman a,1, Karen L. Jaunarajs a, Qin Wang b, David G. Standaert a, Lori L. McMahon b,*

a Department of Neurology, Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham, Birmingham, AL 35294, USA
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Methods

- DYT1 mutant knock-in mice (TorA^{ΔE/+})
- Littermate controls (TorA^{+/+})

- Microdialysis cannula implanted near striatum
  - Baseline samples for basal levels of ACh
- Sacrificed mice, evaluated brain slices
  - Assessed activity of AChI: patch clamp

Scarduzio et al. Exp Neurol 2017
Results

- Baseline levels of ACh tone in cannulated mice
  - Extracellular striatal acetylcholine increased in TorA^{ΔE/+} vs TorA^{+/+} mice

Scarduzio et al. Exp Neurol 2017
D2R activation of slices (quinpirole) with paradoxical increase in Chl firing in striatum of TorAΔE/+ compared to suppression in controls

Scarduzio et al. Exp Neurol 2017
Altering ACh tone pharmacologically

- Reduction of cholinergic tone (ACh Antagonists (scopolamine)) reversed the D2R paradoxical excitation in Chls in TorA^{ΔE/+} mice

- Increasing cholinergic tone (neostimine) in wild type mice (TorA^{+/+}) caused the same paradoxical response (increased firing of AChI) to dopaminergic stimulation seen in TorA^{ΔE/+} mice

Scarduzio et al. Exp Neurol 2017
A model of DYT1 dystonia?

Scarduzio et al. Exp Neurol 2017
Summary

- There is an intrinsic hypercholinergic state in DYT1 mouse model

- There is a novel interaction between muscarinic AChRs and dopaminergic D2Rs in modulating striatal excitability

- Interventions targeted at the primary defect in hypercholinergic tone and downstream alterations in striatal signaling provide potential therapeutic targets for pharmacologic interventions

Scarduzio et al. Exp Neurol 2017
Downs a et al. Neurobiol Dis 2019
Cerebellum in dystonia
Evidence for involvement of cerebellum in dystonia

- Case reports focal lesions of cerebellum cause dystonia
- Abnormal eyeblink conditioning (cerebellar sign) in focal dystonia
- Abnormal saccadic adaptation (cerebellar sign) in DYT11 dystonia
- Subtle anatomic defects in Purkinje cells
- Functional imaging with abnormalities in cerebellum
- Animal models
- Abnormal cerebellar connectivity and plasticity in CD

Shakkottai et al. Cerebellum 2017
Bologna and Berardelli. Cerebellum & Ataxias 2017
Porcacchia et al. PLOS one 2019
Cerebellum and CD

- Tremor dominant CD
  - Cerebellar involvement
    - Axial cerebellar disability
    - Atrophy of cerebellar vermis
    - Abnormal processing of proprioceptive (not tactile) information in defective corticocerebellar loop

Mahajan A et al. Cerebellum 2021
Avanzino L et al. Neurology 2020
Is activation of the cerebellum involved in dystonia?

- Normal mice
- Tottering mice

- Microinjections of agents into midline cerebellum at primary fissure, 4 animals each group

Cerebellum and dystonia

- Dystonia induced by nonspecific hyperexcitability (glutamate receptors)
- Absence of purkinje cells abolishes kainic acid dystonia

- AMPA antagonist reduces kainic acid induced dystonia
- AMPA agonist induced dystonia (dose dependent)

Conclusions

- Glutamate receptor activation in cerebellum is associated with dystonia (nl and tottering mice)
  - Specifically, activation of AMPA receptors (not NMDA receptors)
  - AMPA antagonists alleviate glutamate induced dystonia

- Purkinje cells necessary for this effect
Perampanel (selective AMPA antagonist) in CD Tolerability and safety study

- Open label, Phase 2a study
- 25 CD patients at least 8 weeks from last BoNT
- Open label perampanel titrated to 12 mg per day as tolerated over 6 weeks
- Maintenance for 4 weeks

- 8 withdrawals, 4 for AE
- All patients with drug related AE’s
- Only 20% tolerated dose ≥ 4 mg
- Improved pain and sleep, but no change in TWSTRS motor

Summary

- Dystonia with diverse phenomenology
- New classification system to clarify categorization
- Genetics of dystonia: an ongoing journey of discovery
- Pathophysiology
  - Implicates network disorder, with cerebellum and basal ganglia involvement likely
  - Aberrancies in
    - Cholinergic tone
    - Dopamine receptor sensitivity (D2)
    - AMPA receptors
Our mission is to advance the pace of clinical and translational research in the dystonias to find better treatments and a cure.

H. A. (Buz) Jinnah, MD PhD
Director, The Dystonia Coalition
Emory University School of Medicine
Collaboration of medical researchers and patient advocacy groups (PAG)

- 49 clinical centers in the United States, Canada, Australia, France, Germany, Italy, and the UK.

Studies
- Natural history (over 3000 patients included)
- Biobank project
- Patient-centered outcomes
- Objective measures projects

The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies

Gamze Kilic-Berkmen¹, Laura J. Wright², Joel S. Perlmutter³, Cynthia Comella⁴, Mark Hallett⁵, Jan Teller³, Sarah Pirio Richardson⁶, David A. Peterson⁷, Carlos Cruchaga⁸, Codrin Lungu⁹ and H. A. Jinnah¹¹

REVIEW
published: 08 April 2021
Formed in 1976 by Sam & Fran Belzberg when their daughter, Cheri was finally diagnosed with dystonia

First & largest dystonia patient organization in the world addressing the needs of those affected by all forms of dystonia

DMRF Mission: Advance research that will lead to more effective treatments and ultimately a cure; Promote awareness and education; and To support the well being of affected individuals and families.
The Dystonia Medical Research Foundation

- Devoted to
  - Education
  - Research
  - Awareness
  - Advocacy
- New journal: Dystonia
  - Aasef Shaikh, MD, PhD & Roy V. Sillitoe, PhD.
Dystonia patient advocacy and research foundations
Funding for dystonia research

- Dystonia Coalition
  - Career development
  - Pilot projects Grown from 8 Sites to Many

- Dystonia Medical Research Foundation
  - Research awards annually

- AAN
  - Clinical investigator awards

- NIH
  - K23
  - K08
  - R01