Treatment of Dystonia

Joseph Jankovic, MD

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Guiding Principles in the Treatment of Dystonia

- **Identify a specifically treatable cause (e.g. Wilson's disease, drugs, structural lesions, metabolic abnormalities, vitamin/biotin deficiency)**
- Educate patient and family (genetic counseling)
- Address co-morbidities (pain, depression, orthopedic complications)
- Explain that therapy for dystonia is symptomatic not neuroprotective
- Select treatment according to severity, age, type, and distribution
- Encourage patients to discover alleviating maneuvers (sensory tricks)
- Range of motion exercises to prevent contractures
- Levodopa in childhood- and young-onset dystonia
- Most treatments are based on empirical observations and experience (DBPC studies are needed)
- Surgical therapy should be reserved for patients with disabling dystonia resistant to pharmacological and/or BoNT therapy

Treatable Inherited Rare Movement Disorders

H. A. Jinnah, MD, PhD,[1*] Alberto Albanese, MD,[2,3] Kailash P. Bhatia, MD,[4] Francisco Cardoso, MD,[5] Gustavo Da Prat, MD,[6,7] Tom J. de Koning, MD, PhD,[8] Alberto J. Espay, MD,[9] Victor Fung, PhD, FRACP,[10] Pedro J. Garcia-Ruiz, MD,[11] Oscar Gershanik, MD, PhD,[12] Joseph Jankovic, MD,[13] Ryuji Kaji, MD, PhD,[14] Katya Kotschet, MD,[15] Connie Marras, MD, PhD,[16] Janis M. Miyasaki, MD, MEd,[17] Francesca Morgante, MD,[18] Alexander Munchau, MD,[19] Pramod Kumar Pal, MBBS, MD, DM,[20] Maria C. Rodriguez Oroz, MD,[21,22,23,24] Mayela Rodríguez-Violante, MD,[25] Ludger Schöls, MD,[26,27] Maria Stamelou, MD,[28,29] Marina Tijssen, MD, PhD,[30] Claudia Uribe Roca, MD,[31] Andres de la Cerda, MD,[32] Emilia M. Gatto, MD,[33]
for the International Parkinson's Disease Movement Disorders Society Task Force on Rare Movement Disorders

Mov Disord 2018;33:21-35

Vitamins
- abetalipopreteinemia
- ataxia Vit E deficiency
- biotinidase deficiency
- cerebral folate deficiency
- cobolamin deficiency
- CoQ10 deficiency
- Homocysteinuria
- PDH deficiency

Target reduction
- CTX
- Manganese transporter
- Niemann Pick C
- Wilson's disease

Dietary interventions
- abetalipoproteinemia
- GLUT1
- glutaric aciduria
- homocystinuria
- MSUD
- methylmalonic aciduria
- phenylketonuria
- propionic academia
- Refsum

Trigger avoidance
- alternating hemiplegia
- thiamine transporter
- glutaric aciduria
- MSUD
- methylmalonic aciduria
- proplonic academia
- rapid-onset D-P

Specific drugs
- AADC deficiency
- DRD
- EA-2
- MOCS1
- PKD
- PTPS

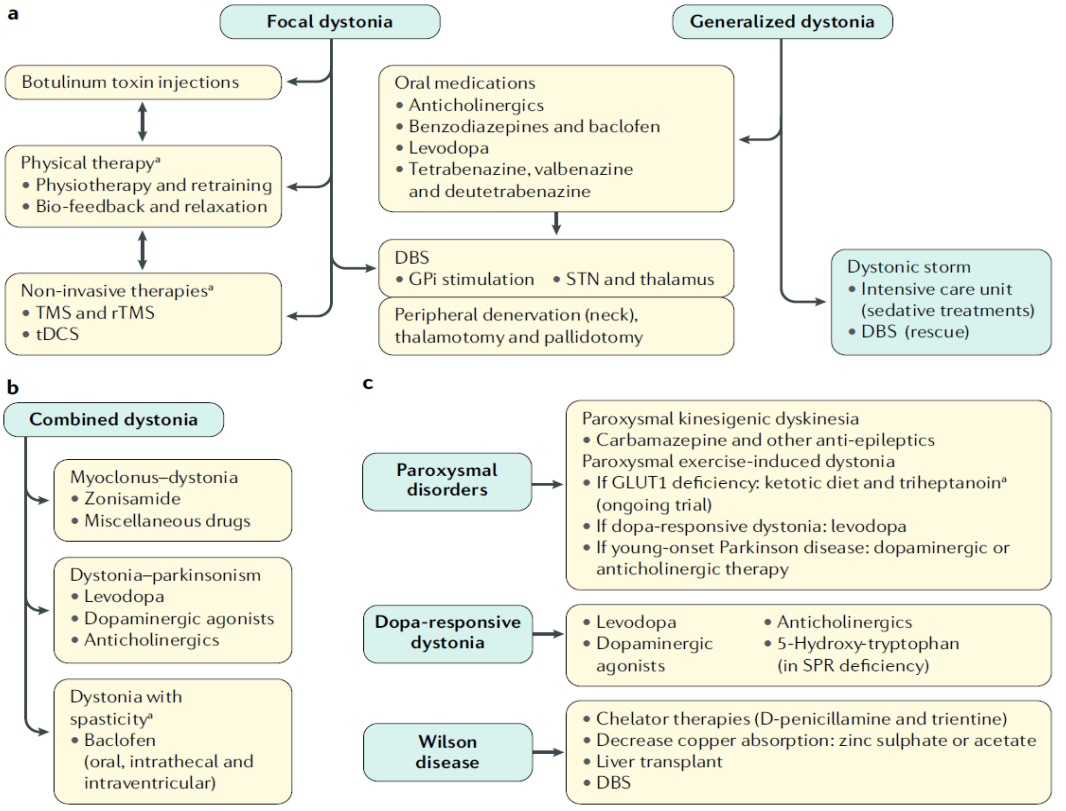
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Treatment algorithm for dystonia



Balint B, Mencacci NE, Valente EM, Pisani A, Rothwell J, Jankovic J, Vidailhet M, Bhatia KP. Dystonia. Nat Rev Dis Primers 2018;4:25

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Dystonia rating scales

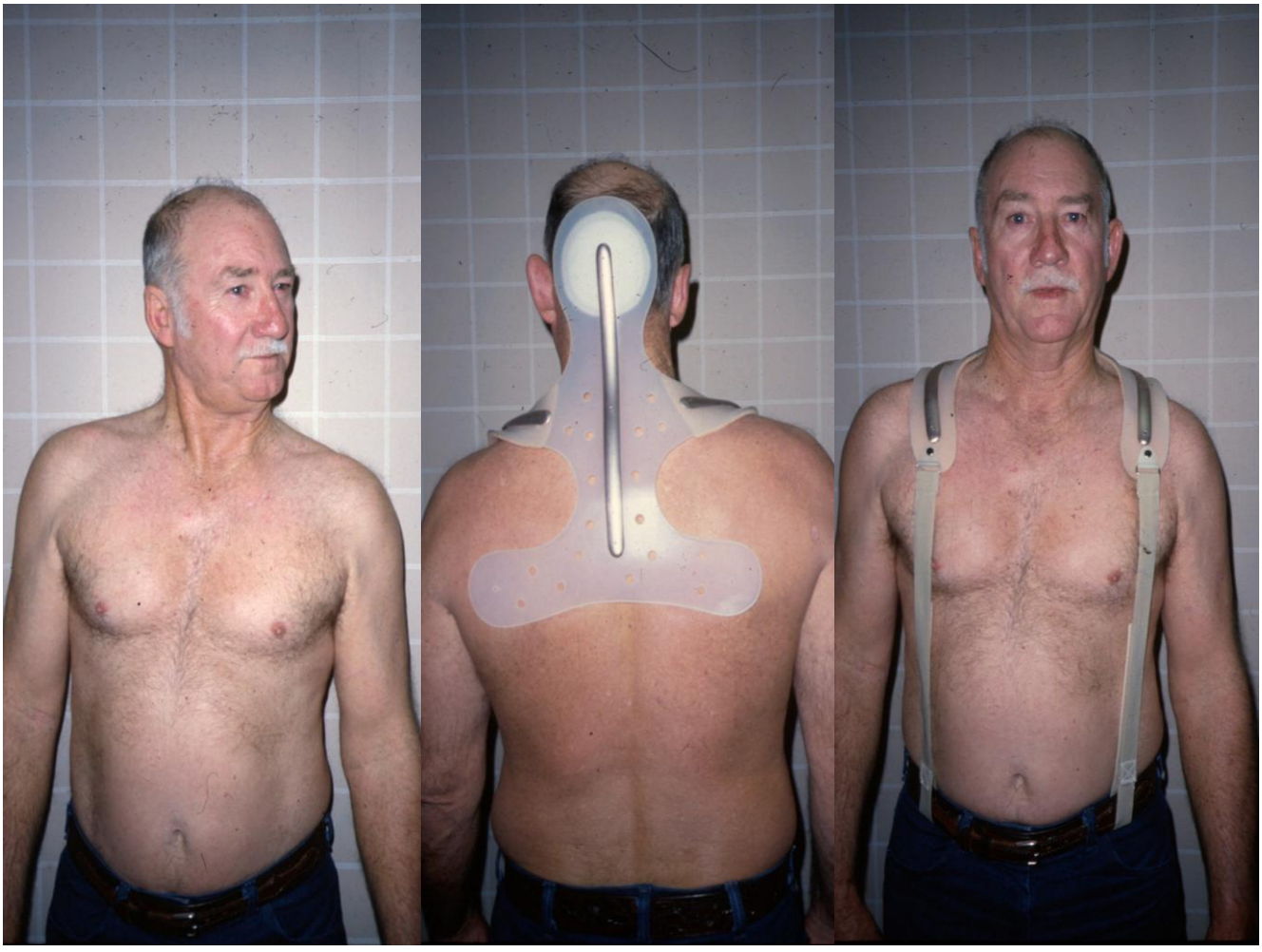
Scale	Patient historical rating	Clinical examination
BSDI	Yes	No
Jankovic rating scale	No	Yes
Blepharospasm Disability Scale	Yes	Yes
CDIP-58	Yes	No
Functional Disability Questionnaire	Yes	No
TWSTRS	No	Yes
Tsui scale	No	Yes
Modified Tsui scale	No	Yes
Freiberg Questionnaire for Dystonia torticollis version	Yes	No
Disability questionnaire for patients with cervical dystonia	Yes	No
Body Concept Scale	Yes	No
Ways of Coping Checklist	Yes	No
CDQ-24	Yes	No
Oromandibular dystonia questionnaire	Yes	No
Unified Spasmodic Dysphonia Rating Scale	No	Yes
VHI	Yes	Yes
Voice Handicap Index 10	Yes	No
Voice-Related Quality of Life	Yes	No
VPQ	Yes	No
Arm Dystonia Disability Scale	Yes	No
Dystonia Evaluation Scale	Yes	No
Tubiana–Chamagne Score	Yes	No
Writer's Cramp Rating Scale	No	Yes
Global Dystonia rating Scale	No	Yes
BFMDRS	Yes	Yes
Unified Dystonia Rating Scale	Yes	Yes

BFMDRS, Burke-Fahn–Marsden Dystonia Rating Scale; BSDI, Blepharospasm Disability Index; CDIP-58, Cervical Dystonia Impact Profile; CDQ-24, Craniocervical Dystonia Questionnaire; N/A, not applicable; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; VHI, Voice Handicap Index; VPQ, Vocal Performance Questionnaire.

Pietracupa et al. J Neurol Sci 2015;358:9–21

Therapy of Dystonia

- **Pathogenesis-targeted or disease-modifying therapies**
  (e.g. autoimmune, DRD, drugs, metabolic, structural lesions, WD)
- **Symptomatic therapies**
  - **Physical, supportive, and ancillary therapy**
  - **Drug treatment (including IT baclofen)**
  - **Chemodenervation with botulinum toxin**
  - **Surgery: peripheral, central**



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DOPA-Responsive Dystonia (DRD)

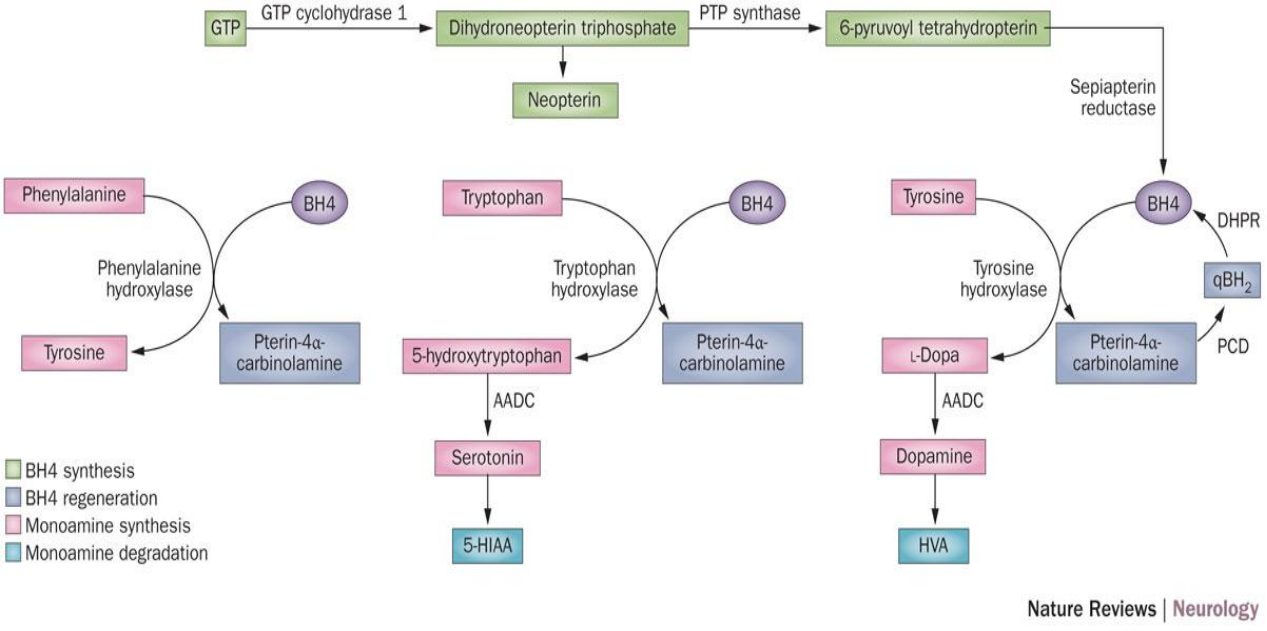
- **Age at onset: 1- 15 yrs, F > M**
- **Typically presents with stiff-legged, toe-walking gait, balance problems**
- **Better after sleep, worst at the end of the day; diurnal variation in 50%**
- **Other features: parkinsonism, focal dystonia, rest/postural tremor, myoclonus, scoliosis, spastic paraparesis, depression, anxiety, deafness, infantile hypotonia (often misdiagnosed as CP)**
- **May have FHx of "Parkinson's disease"**
- **F-DOPA PET is normal (but abnormal with PD phenotype)**
- **AD, >100 mutations identified in the *GCH1* gene (14q22.1) that codes for GTP-cyclohydrolase, incomplete penetrance (higher in women)**
- **There are many other causes of DRD: tyrosine hydroxylase (TH), sepiapterin reductase (SPR), 6-pyruvoyl tetrahydropterin synthase (PTS) deficiency**
- **Responds to low doses of levodopa, dopamine agonists, anticholinergics; dyskinesias are uncommon**
- **Because of the possibility of DRD, all children with dystonia should be initially treated with levodopa**

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Dopa-responsive dystonia-clinical and genetic heterogeneity.

Wijemanne S, Jankovic J. Nat Rev Neurol 2015;11:414-24

Biosynthesis of tetrahydrobiopterin (BH4) and monoamine neurotransmitters



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Treatment options for dystonia

Pharmacological therapies

- **Levodopa** (in DRD, *GNAO1, CTNNB1,etc)*
- **Anticholinergics** (trihexyphenidyl)
- **Baclofen** (oral, IT, intraventricular)
- **Dopamine-depleting drugs**
  - **Tetrabenazine**
  - **Deutetrabenazine**
  - **Valbenazine**
- **Dopamine receptor blocking drugs**
  - Clozapine
- **Benzodiazepines** (diazepam, clonazepam, lorazepam, midazolam)
- **Muscle relaxants** (cyclobenzaprine, tizanidine, metaxalone, carisoprodol, methocarbamol, chlorzoxazone)
- **Zolpidem**
- **Apraclonidine, Oxymetazoline eye drops**
- **Sodium oxybate (GABA analog)**
- **Anticonvulsants**
  - phenytoin, carbamazepine, oxcarbazepine, levatiracetam, valproic acid, zonisamide, gabapentin, pregabalin
- **Theophylline/caffeine** for *ADCY5*-related dyskinesia
- **Botulinum toxin**
  - OnabotulinumtoxinA
  - AbobotulinumtoxinA
  - IncobotulinumtoxinA
  - DaxibotulinumtoxinA
  - RimabotulinumtoxinB
- **Surgical therapies**
  - **Deep brain stimulation**
    - GPi, STN, Cerebellum
  - **Ablative surgeries**
    - Pallidotomy, Thalamotomy
    - Focused Ultrasound

Most treatments are based on case reports, empirical observations, or open-label trials

Bansal D, Jankovic J. Emerging Treatments for Dystonia. Expert Opinion on Emerging Drugs 2026 (in press).

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Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl.

Burke RE, Fahn S, Marsden CD. Neurology 1986;36:160-4

- **31 patients completed the protocol**
- **Mean age 18.6 years (range: 9-32 years)**
- **Mean duration of dystonia 9.7 years (range: 0.3 - 22 years)**
- **Videos rated using the Burk-Fahn-Marsden scale**
  Burke et al. Neurology 1985;35:-73-7

- **22 (71%) had a clinically significant response**
- **After a mean follow-up of 2.4 years, 68% of patients continued to take trihexyphenidyl, and 42% continued to show a considerable or dramatic benefit**
- **At a mean daily dose of 40 mg (5-120 mg) the drug was generally well tolerated**
- **High-dosage trihexyphenidyl therapy is effective in the management of torsion dystonia**

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Long-term outcomes of intraventricular baclofen therapy for medically refractory generalized secondary dystonia.

Koueik et al. J Neurosurg Pediatr 2025;35:480-5

- **Retrospective analysis included 27 patients (median age 12.9 years); 21 (78%) with CP.**
- **The follow-up duration ranged from 1.2 to 16.7 years, with a median of 7.7 years and mean of 8.4 years.**
- **The baclofen dosage was twice as high in patients with metabolic and neurodegenerative disorders compared with those with CP, TBI, and infection, with median dosages of 1455 µg/day and 725 µg/day, respectively.**
- **Both post-treatment Barry-Albright Dystonia Scale and Ashworth Scale scores showed statistically significant improvement.**
- **Complications included infection that necessitated pump removal in 1 patient (4%), wound dehiscence that was treated with wound revision and antibiotics in 1 patient (4%), and hydrocephalus that required CSF diversion in 4 patients (15%).**
- **In 2 patients, IVB therapy was ineffective at controlling dystonia and, thus, was discontinued after 1.3 and 2.7 years.**

An Open-Label Pilot Study to Examine the Safety, Tolerability and Efficacy of Deutetrabenazine in Isolated Dystonia.

Deik et al. Mov Disord Clin Pract 2025;12:504-9

Participant	Age/ Gender	Dystonia distribution	PGI-C[a]	Blinded CGI-C[b]	PGI-C/ CGI-C agreement	Blinded GDS (SC)	Blinded GDS (EM/T)	Blinded GDS % change[c]	PGI-C/ CGI-C/ GDS agreemen
1	71/F	Focal (CD)	3 (I)	3 (I)	Yes	2	2	0	No
2	69/M	Focal (CD)	4 (N)	4 (N)	Yes	6	6	0	Yes
3	60/M	Focal (CD)	4 (N)	5 (W)	No	4	4	0	No
4	29/F	Segmental (cra-lar-bra)	3 (I)	4 (N)	No	24	25	+4.2	No
5	68/M	Segmental (cra-cerv)	4 (N)	5 (W)	No	11	12	+9.1	No
6	45/M	Focal (CD)	5 (W)	6 (W)	Yes	8	13	+62.5	Yes
7	57/F	Segmental (cra-cerv)	2 (I)	3 (I)	Yes	14	13	−7.1	Yes
8	72/F	Segmental (cra-cerv)	2 (I)	5 (W)	No	7	9	+28.6	No
9	65/F	Segmental (cra-cerv-bra)	3 (I)	4 (N)	No	5	5	0	No
10	63/F	Focal (Bleph)	1 (I)	2 (I)	Yes	24	12	−50	Yes
11	74/F	Focal (CD)	4 (N)	6 (W)	No	3	6	+100	No
12	54/F	Multifocal (Bi-bra)	4 (N)	3 (I)	No	8	8	0	No
13	51/F	Focal (leg)	4 (N)	5 (W)	No	3	5	+66. 7	No
14	68/F	Segmental (cerv-lar)	5 (W)	3 (I)	No	10	8	−20	No
15	57/F	Segmental (cra-cerv-lar)	2 (I)	3 (I)	Yes	22	20	−9.1	Yes

"… those with blepharospasm may have benefited from its use."

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Zolpidem for Treatment of Dystonia

Author	Country	Diagnosis	Age (years)	Sex	Time since diagnosis (years)	Dose per administration (mg)	Average total daily dose (mg)	Outcome	Improved/ Total	Duration of effect (h)	Adverse effects
Evidente (19)	USA	X-linked dystonia parkinsonism ("lubag")	41	M	2	10	80–100	BFMDRS, UPDRS	3/3	2	Sedation if more than 20 mg daily
			36	M	1	10	20			3	
			38	M	1	10	20			2	
Garreto et al. (11)	Argentina	Meige syndrome	57	F	11	10	70	Observation	3/3	3	None
		Blepharospasm	63	M	8	10	30			3	Mild sedation
		Meige syndrome	66	M	22	10	20			3	None
Vazquez-Delgado and Okeson (12)	USA	Oromandibular dystonia	59	F	5	10	10	Observation	1/1	N/A	None
Seo and Jeong (13)	Korea	Dystonia - segmental axial	35	N/A	2	10	10	Observation	1/1	N/A	Mild visual dimness
An et al. (14)	Korea	Meige syndrome	59	M	11	12.5 (CR)	50	Observation	1/1	4	None
Park et al. (15)	Korea	Myoclonus-dystonia syndrome	36	F	16	10	40	Observation	1/1	6	None
Sunwoo (16)	Korea	Blepharospasm	74	F	20	10	10	Observation	1/1	5	None
Miyazaki et al. (5)	Japan	Generalized dystonia	38.3 ± 19.4	3M/6F	4.6 ± 6.8	10	12.2 ± 6.	BFMDRS	3/9	N/A	Sedation (8 out of 34 total patients, 3 out of 8 zolpidem responders)
		Meige syndrome/ blepharospasm	60.6 ± 9.6	6M/4F	3.6 ± 3.2	10	12.0 ± 4.8		2/10		
		Cervical dystonia	45.7 ± 14.4	7M/0F	6.0 ± 4.9	10	10 ± 0		0/7		
		Hand dystonia	48.4 ± 10.1	5M/3F	7.4 ± 5.2	10	8.8 ± 5.1		3/8		
Waln and Jankovic (17)	USA	Blepharospasm	67	F	17	10	25	Observation	1/1	N/A	None
Miyazaki et al. (6)	Japan	Isolated dystonia	35	M	15	10	20	BFMDRS	2/2	4	Sedation if 20 mg single dose was used
			20	M	6	10	20			3	
Martinez-Ramirez et al. (18)	USA	Oromandibular dystonia	52	M	3	10	15	Observation	1/1	3	None

CR, zolpidem continuous release formulation; N/A, information not available or not reported; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Zolpidem acts on the GABA-A receptors facilitating inhibitory pathways in the basal ganglia motor loop

Badillo SPJ, Jamora RDG. Front Neurol 2019;10:779

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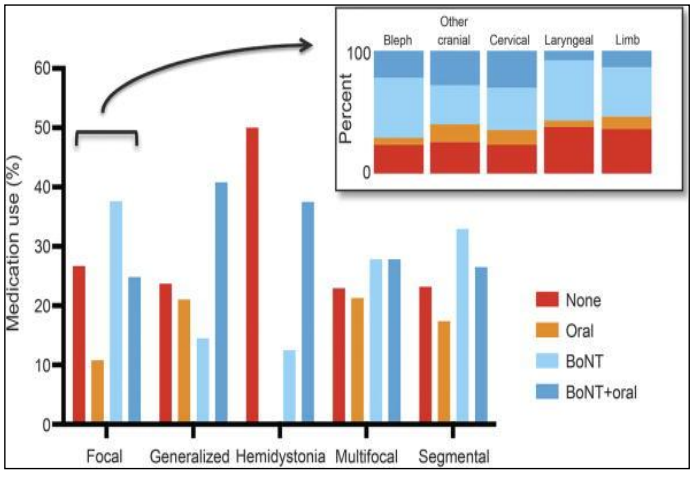
Bansal D, Jankovic J. Emerging Treatments for Dystonia. Expert Opinion on Emerging Drugs 2026 (in press).

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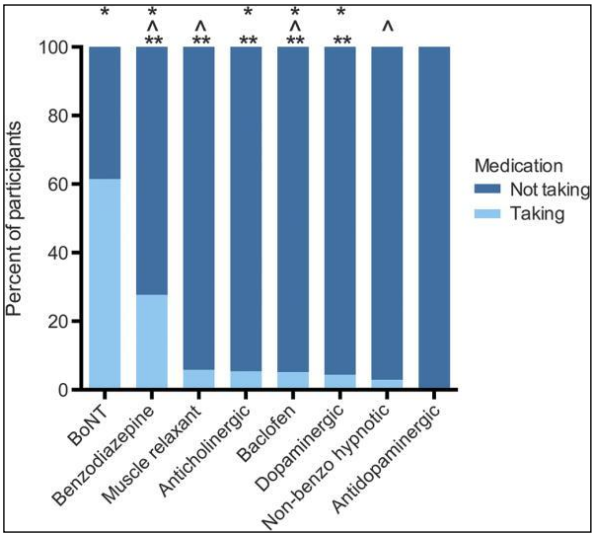
Dystonia treatment:
Patterns of medication use in an international cohort.

Pirio Richardson et al. Neurology 2017;88:543-50

Medication use by dystonia type and subtype



Medication use by class



- **2,026 participants with isolated dystonia at 37 Dystonia Coalition sites**
  - **Focal dystonia (76.4%; CD - 60.9%), segmental dystonia (16.4%), generalized dystonia (3.8%), multifocal dystonia (3%), hemidystonia (0.4%)**
- **1,488 (73%) used medications for dystonia; 61% of the total sample used BoNT therapy alone or in combination**

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https://blepharospasm.org

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Sculpture Garden, Jeju Island, South Korea

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Psychological torture scene from *A clockwork Orange*

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Treatment of Blepharospasm

- **Alleviating maneuvers (sensory tricks)**
- **Devices: Eyelid crutches, goggles, gray or FL-41 tinted lenses**
- **Treatment of dry eyes and blepharitis: artificial tears, ointment, hypotonic 0.18% sodium hyaluronate, cyclosporin 0.05% (Restasis), Xiidra ophthalmic solution (lymphocyte function-associated antigen 1 antagonist)**
- **Medical therapies: clonazepam, anticholinergics, baclofen, levatiracetam, cyproheptadine, methylphenidate, VMAT2 inhibitors, etc**
- **Alpha-2 adrenergic receptor agonists: stimulate contraction of superior tarsal (Müller) muscle (effective in blepharospasm and ptosis)**
  - **Apraclonidine ophthalmic solution**
    Vijayakumar D, Wijemanne S, Jankovic J. J Neurol Sci 2017;372:57-9
  - **Oxymetazoline hydrochloride ophthalmic solution (UPNEEQ)**
    Sung et al. J Med Case Rep 2022;16:299
- **BoNT = treatment of choice**
- **Surgery**
  - **Peripheral**
  - **Central**

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Alleviating maneuvers in blepharospasm



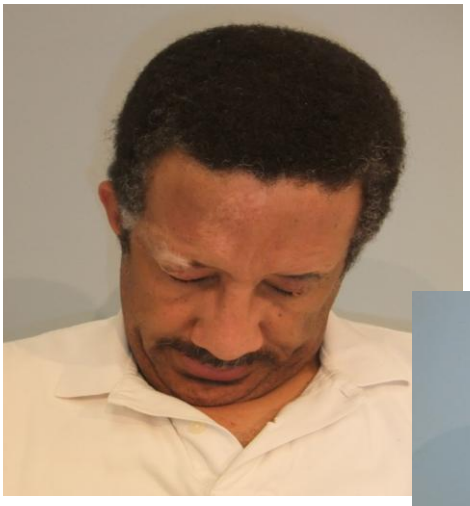
ALLEVIATING MANEUVERS

A. Blepharospasm – trying to open R eye by opening L eye
B. Able to open his eyes by touching his eyebrow
C. Able to open his eyes with the use of yellow tinted lenses

Patel N, Jankovic J, Hallett M. Sensory aspects of movement disorders. Lancet Neurol 2014;13:100-12
Patel N, Hanfelt J, Marsh L, Jankovic J; Dystonia Coalition. Alleviating manoeuvres (sensory tricks) in cervical dystonia. JNNP 2014;85:882-4

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Alleviating Maneuvers



Blepharospasm
Anterocollis
Laterocollis





Patel et al.
Lancet Neurol 2014;13:100-12
Patel et al.
JNNP 2014;85:882-4

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Eyelid Crutch for Ptosis (Droopy Eyelids)

www.eyeglassrepair.net

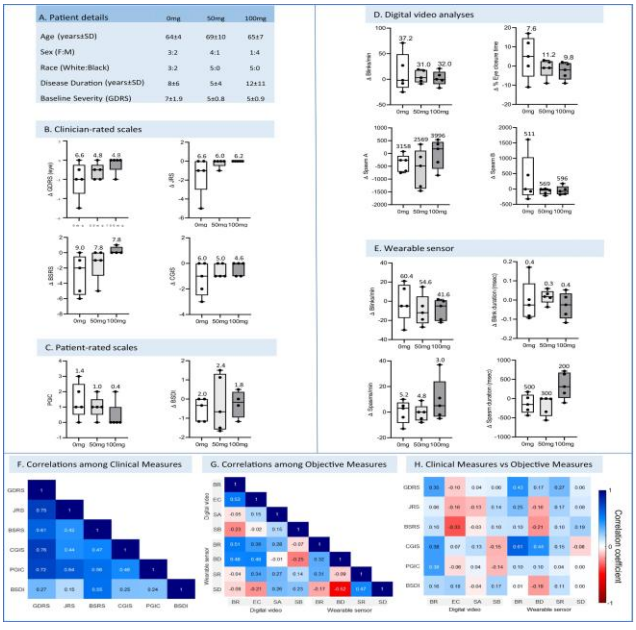


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An Exploratory, Randomized, Double-Blind Clinical Trial of Dipraglurant for Blepharospasm.

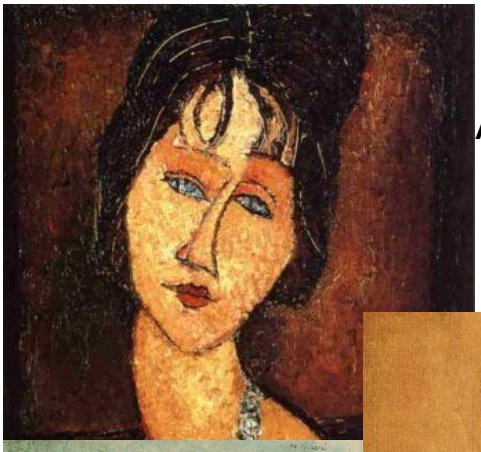
Kilic-Berkmen et al. Mov Disord 2024;39:738-45

- **Dipraglurant is an oral allosteric inhibitor of mGluR5 (metabotropic glutamate receptor type 5), expressed in regions of the brain thought to contribute to dystonia.**
- **Dipraglurant reversed abnormal excitability in a mouse model of *TOR1A*-related dystonia and in a rat model of *GNAL*-related dystonia.**
- **Phase 2a, RDBPC trial of 15 participants who were assigned to receive a placebo or dipraglurant (50 or 100 mg) and assessed over 2 days, 1 and 2 hours following dosing.**
- **Although dipraglurant appeared well tolerated, it did not produce a trend for clinical benefit.**



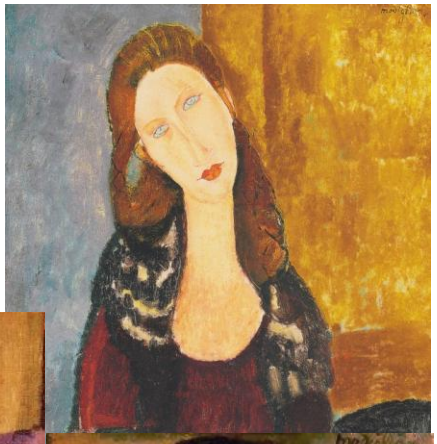
Global Dystonia Rating Scale (GDRS), Jankovic Rating Scale (JRS), Blepharospasm Severity Rating Scale (BSRS), Clinical Global Impression of Severity (CGIS), Blepharospasm Disability Index (BSDI), Participant Global Impression of Change (PGIC)

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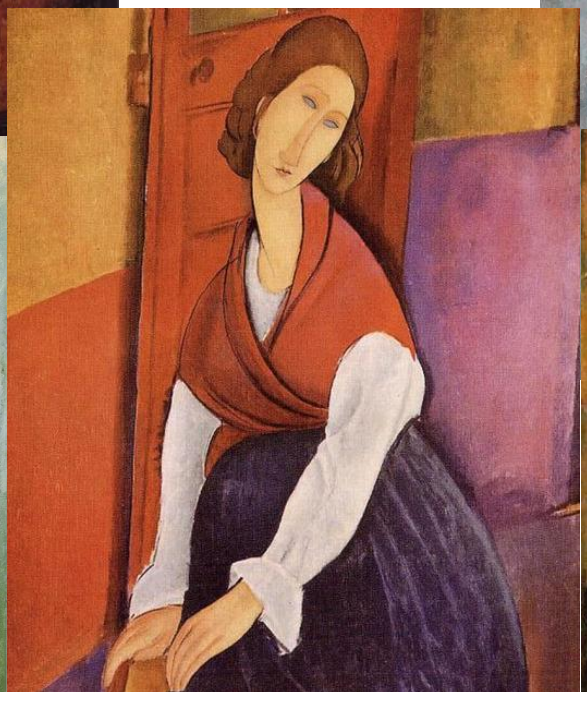


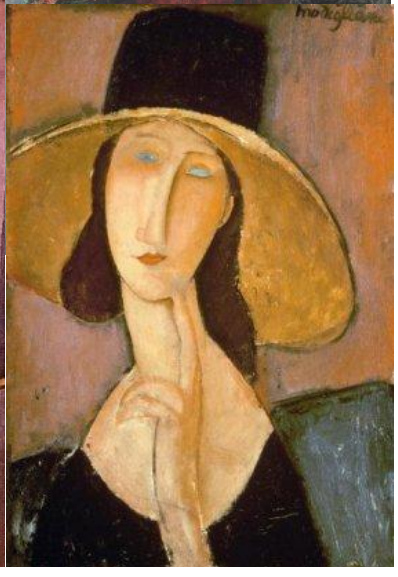
Cervical Dystonia

Amedeo Clemente Modigliani
(1884 –1920)



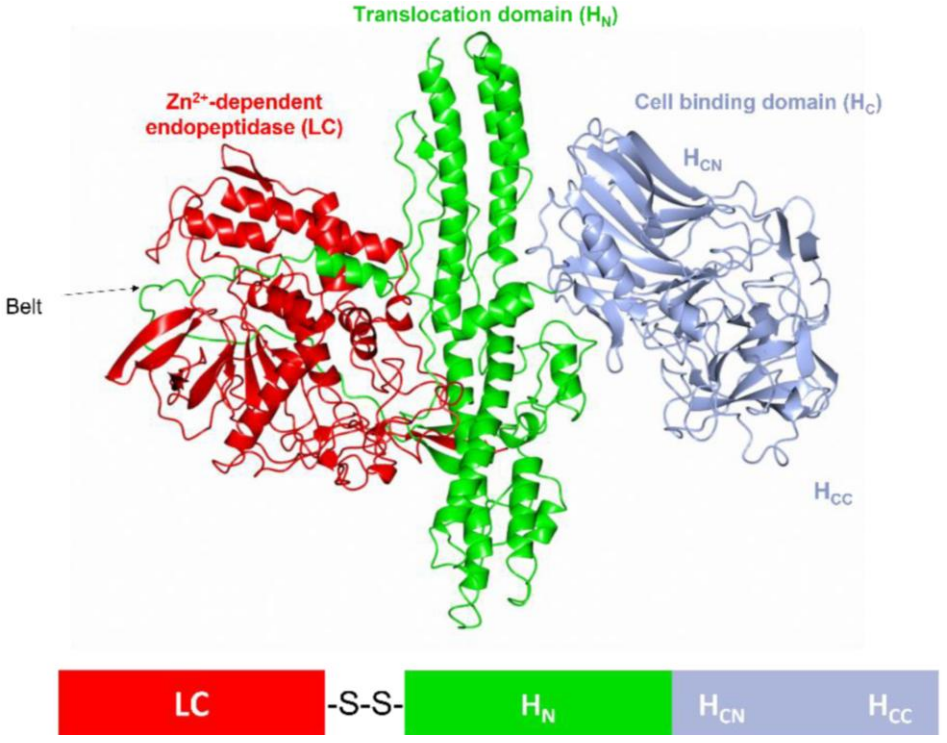






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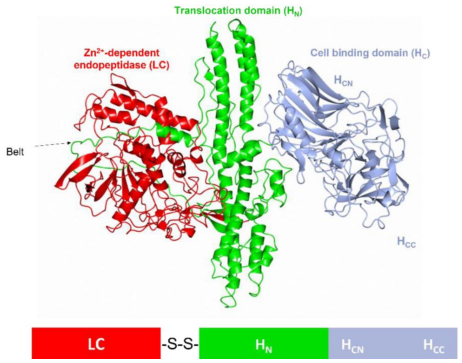
Functional Domains of Botulinum Toxin

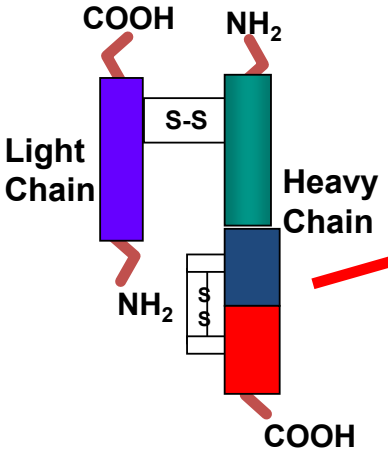


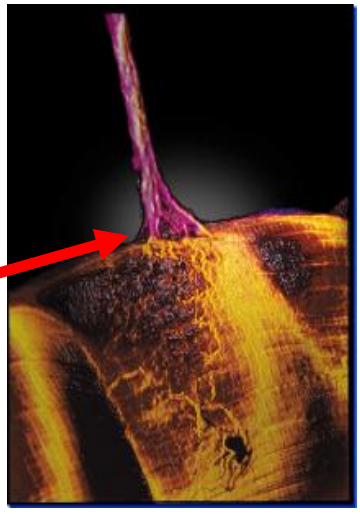
Lacy DB, Tepp W, Cohen AC, DasGupta BR, and Stevens RC. Crystal structure of botulinum neurotoxin type A and implications for toxicity. Nat Struct Biol 1998;5:898–902

35

Botulinum Toxin Mechanism of Action



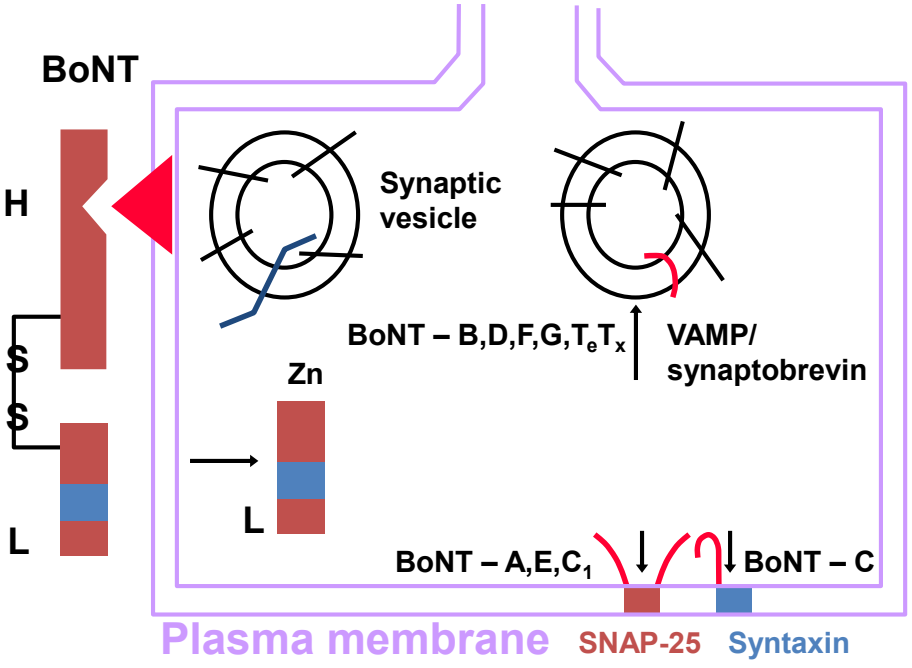




Local, Temporary Cholinergic Chemodenervation

36

Botulinum Toxin Targets at the Nerve Terminal

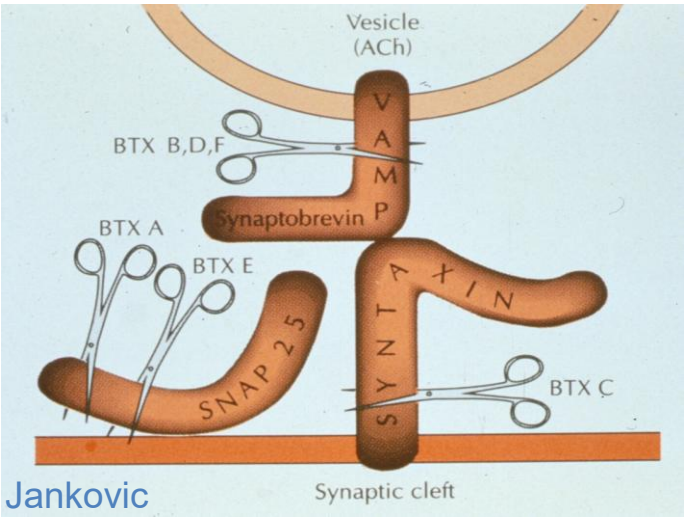


Jankovic. J Neurol Neurosurg Psychiatry 2004;75:951-7

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Botulinum Neurotoxin Toxin (BoNT) Serotypes: Cleavage of SNARE Proteins

Toxin Type	Substrate
BoNT/A	SNAP-25
BoNT/B	VAMP/Synaptobrevin
BoNT/C	Syntaxin, SNAP-25
BoNT/D	VAMP/Synaptobrevin
BoNT/E	SNAP-25
BoNT/F	VAMP/Synaptobrevin
BoNT/G	VAMP/Synaptobrevin
BoNT/H	VAMP/Synaptobrevin

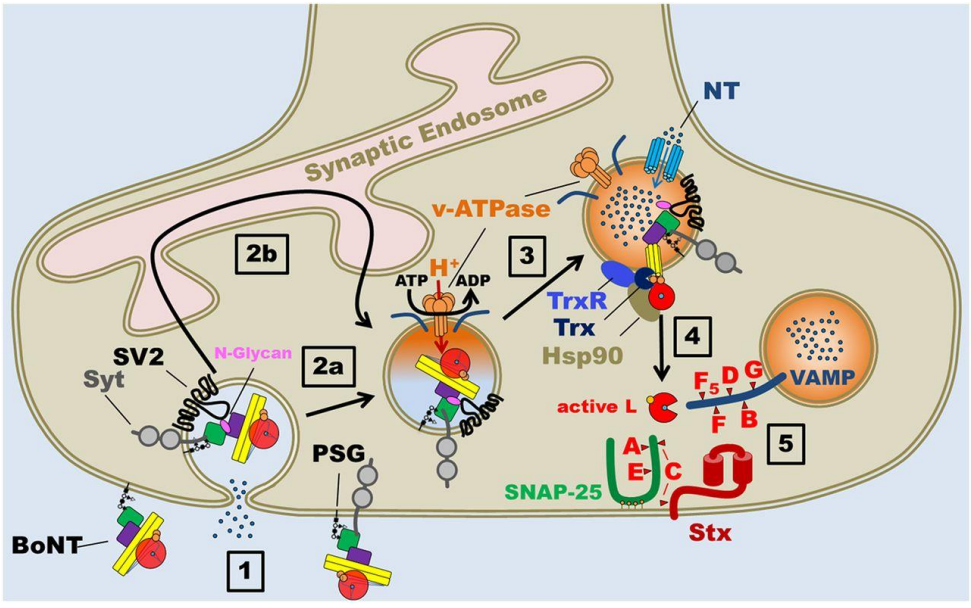


Soluble N-ethylmaleimide-sensitive Factor Activating Protein Receptor (SNARE) proteins

SNAP-25 = synaptosomal-associated protein 25
VAMP = vesicle-associated membrane protein

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5-step process of BoNT → chemodenervation

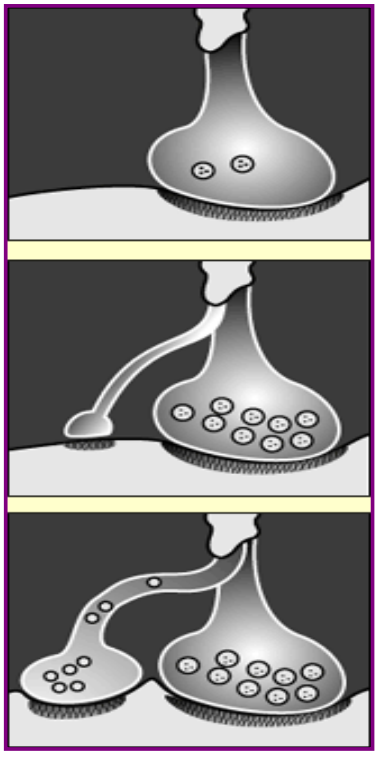


1. Binding of the HC domain to a polysialoganglioside (PSG) receptor at the presynaptic membrane
2. Binding to a protein receptor, either synaptotagmin (Syt) or SV2
3. The BoNT is then endocytosed inside synaptic vesicles (involves the ATPase proton pump)
4. The L chain is released into the cytosol and cleaves the inter-chain disulphide bond
5. The L-chain metalloproteases of BoNT/A and BoNT/E cleave SNAP25, of BoNT/B, BoNT/D, BoNT/F and BoNT/G cleave VAMP, of BoNT/C cleaves both SNAP25 and Syntaxin → inhibition of neurotransmitter release and consequent neuroparalysis (chemodenervation)

Pirazzini et al. Pharmacol Rev 2017;69:200-35

39

Recovery Following Injection



- **Blockade of Ach release by BoNT at the neuromuscular junction induces the formation of an extensive network of extrajunctional nerve-terminal sprouts (within 14 days) that eventually retract and original terminal recover (within 3 months) correlating with full recovery of nerve-evoked muscle contraction**
- **Clinical benefit wanes in approximately 3–6 months**
- **EMG evidence of denervation may persists up to 1 year**

De Piava et al. Proc Natl Acad Sci 1999;96:3200-5
Rogozhin et al. J Physiol 2008;586:3163-82

40

Brand Name Non-proprietary Name	BOTOX Onabotulinum toxinA	DYSPORT Abobotulinum toxinA	XEOMIN Incobotulinum toxinA	MYOBLOC/ NEUROBLOC Rimabotulinum B
How Supplied	 100U 200U	 300U 500U	 50U 100U 200U	 2.5KU 5KU 10KU
Preparation Storage	Vacuum-dried powder Refrigerate Reconstitute with non-preserved 0.9% NaCl Shelf-life: 3 yrs	Lyophilized powder – reconstitute with NaCl Refrigerate Protect from light Ready-to-use liquid (Europe)	Lyophilized powder – reconstitute with NaCl No need to refrigerate Shelf-life: 4 yrs	Injectable solution – no need to reconstitute Refrigerate
Company	Abbvie (Allergan until 2019) Irvine, CA	Ipsen LTD, Slough, Berks, UK; Medicis Pharmaceutical, Scottsdale, AZ	Merz Pharmaceuticals Greensboro, NC	Supernus Pharmaceuticals, Inc Rockville, MD
FDA Approved Indications	CD Strabismus Blepharospasm and VII nerve disorders (HFS) UL and LL spasticity Hyperhidrosis Frown lines - crow's feet Chronic migraines Detrusor overactivity	CD UL and LL spasticity Cosmetic	CD Blepharospasm UL spasticity Adult sialorrhea Frown lines	CD and associated pain Chronic sialorrhea

DYSTONIA

REVIEW
published: 20 September 2022
doi: 10.3389/dyst.2022.10655

Botulinum Toxin in the Treatment of Cervical Dystonia: Evidence-Based Review

*Nadia Hammoud and Joseph Jankovic**

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, United States

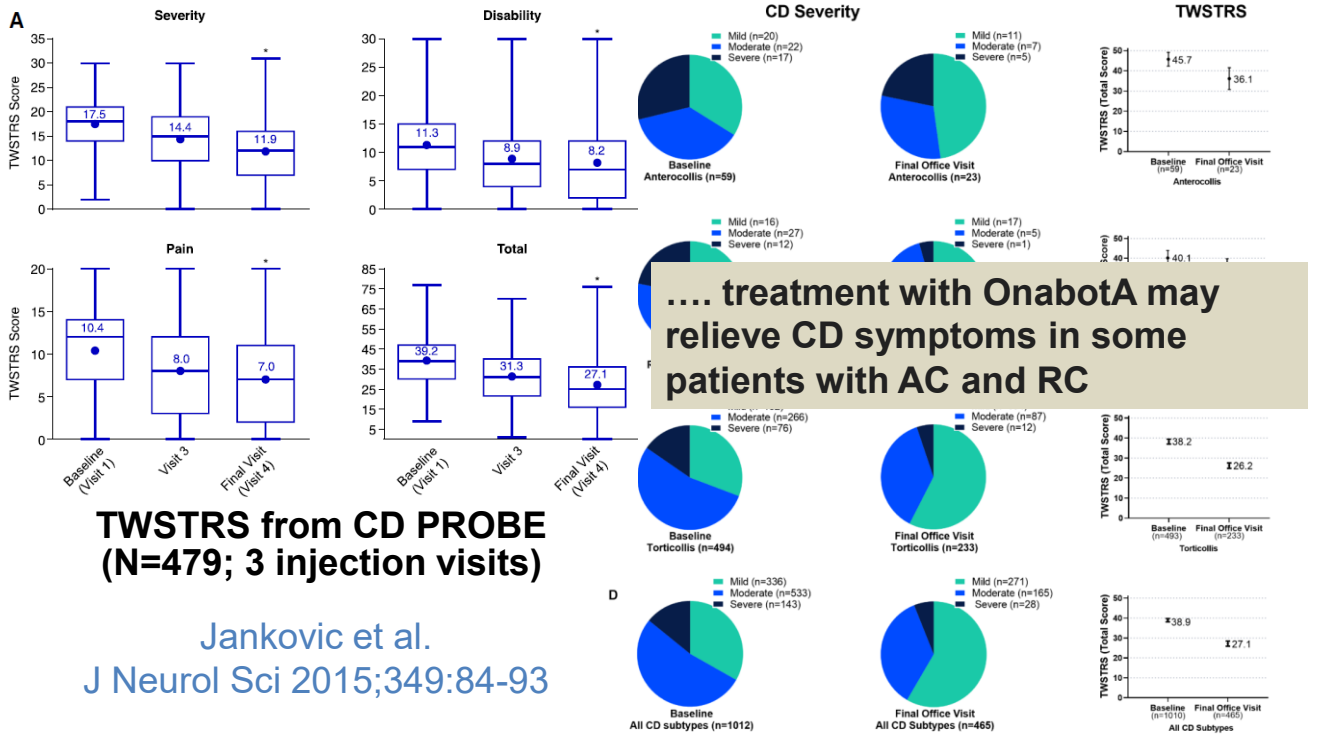
"Patients with predominant anterocollis or retrocollis are often excluded from clinical trials of BoNT because this form of CD is more challenging to treat."

data have demonstrated decades of sustained benefit and safety. Although there is a potential for the development of botulinum toxin immunoresistance, this is quite rare, and partly determined by frequency of administration, cumulative dosage, and properties of the injected product. When immunoresistance does occur, switching to an alternative type of botulinum toxin (e.g., from type A to type B) usually restores the efficacy. In this evidence-based review we highlight the results of published double blind, placebo-controlled studies. We also briefly discuss injection techniques and some unmet needs, such as the development of practical assays to detect immunoresistance and longer-acting formulations of botulinum toxin.

OPEN ACCESS

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Teatment Response to OnabotulinumtoxinA in Cervical Dystonia Patients With Anterocollis and Retrocollis



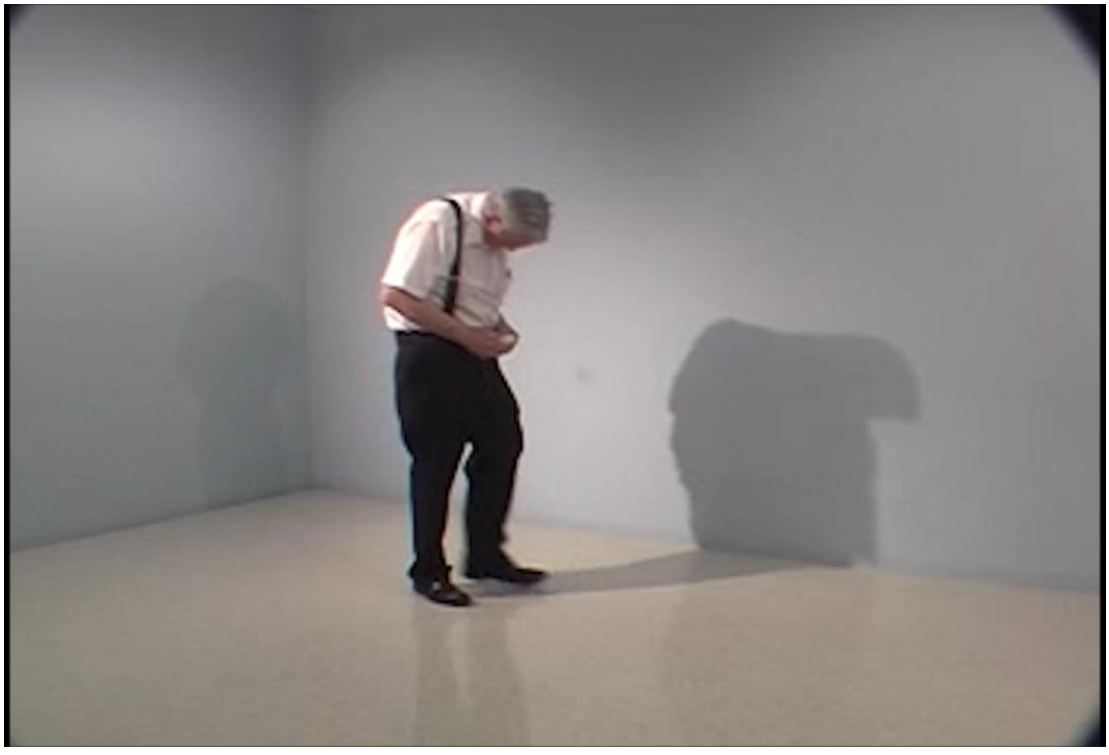
TWSTRS from CD PROBE (N=479; 3 injection visits)

Jankovic et al.
J Neurol Sci 2015;349:84-93

…. treatment with OnabotA may relieve CD symptoms in some patients with AC and RC

Dashtipour et al. Toxicon 2024;248:108035

BoNT in Anterocollis Associated with Parkinson Disease



45

Focal Hand Dystonia, Mirror Dystonia and Motor Overflow

Sitburana O, Jankovic J. J Neurol Sci 2008;266:31-3



49

Injection Techniques

- **Selection of the appropriate target muscles is determined by careful, expert examination**
- **Manual needle placement using anatomical landmarks is used in most cases**
- **EMG – helpful in some cases, but it does not differentiate between agonist and antagonist (compensatory) muscles**
- **Ultrasound – helpful in some cases but …. "there is no difference with regard to a reduction in the severity of cervical dystonia or adverse events between US guided and non-guided injections"**
  Kreisler et al. Rev Neurol (Paris) 2022;178:591-602

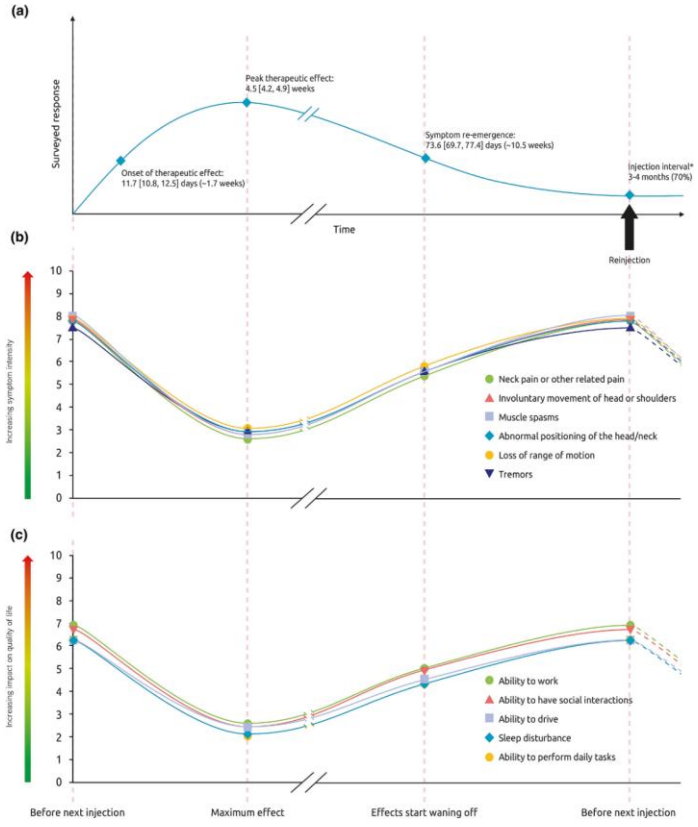
"A fool with a tool is still a fool."



Grady Booch, American Software Engineer

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BoNT Response: Patient Experiences

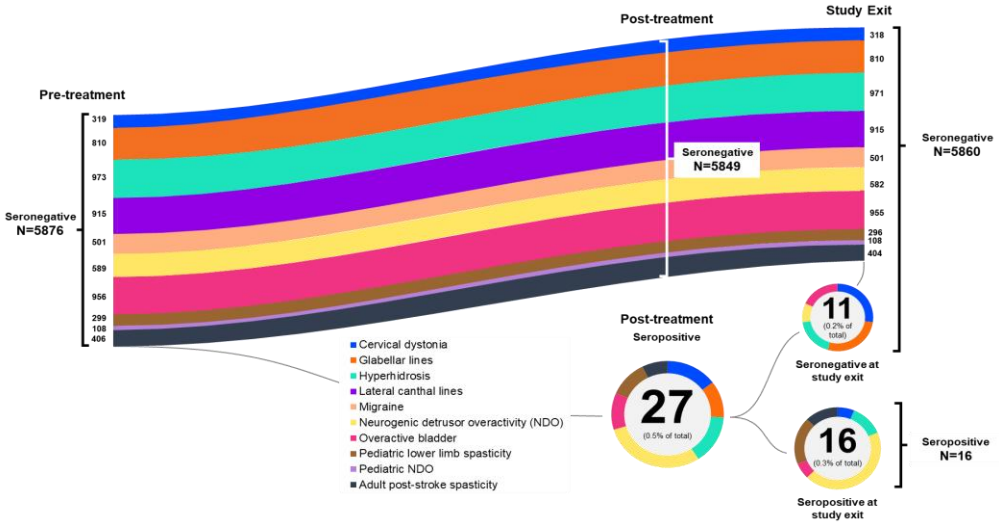


Comella et al. J Neurol 2021;268:903-12

- **Of 209 respondents the mean BoNT-A injection frequency was 3.9 injections/year.**
- **The mean reported onset of BoNT-A therapeutic effect was 11.7 days and the time to peak effect was 4.5 weeks.**
- **The time from injection to symptom re-emergence was 73.6 days (~10.5 weeks).**
- **88% experienced symptom re-emergence between injections.**
- **'Rollercoaster' pattern.**

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Neutralizing antibody status post-treatment and at study exit of subjects who were seronegative at baseline, by indication.



Meta-analysis of 33 prospective placebo-controlled and open-label clinical trials with nearly 30,000 longitudinal subject records prior to and following onabotulinumtoxinA treatment (10U to 600U administered in ≤15 treatment cycles). Overall, 27 of 5876 (0.5%) developed NAbs after onabotulinumtoxinA treatment.

Jankovic et al. Toxins 2023;15:342

55

toxins
2019;11(9)
Review

Immunogenicity Associated with Botulinum Toxin Treatment

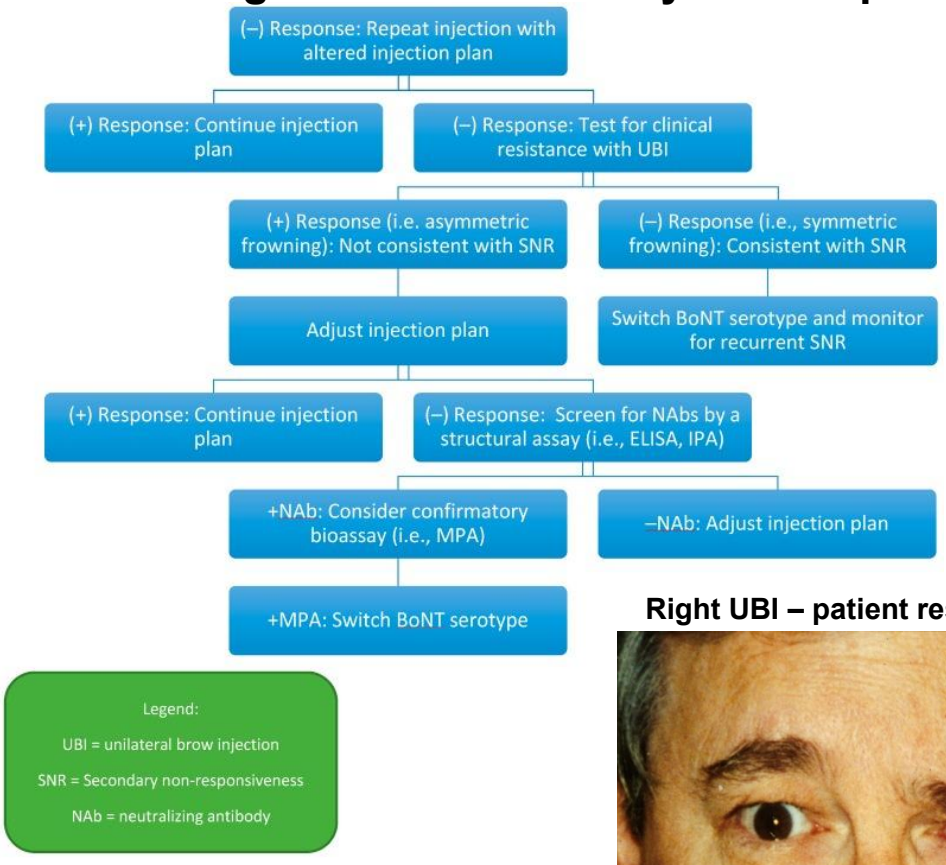
Steven Bellows and Joseph Jankovic *

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA
* Correspondence: josephj@bcm.edu; Tel.: +1-713-798-5998; Fax: +1-713-798-6556

Received: 31 July 2019; Accepted: 22 August 2019; Published: 26 August 2019

Abstract: Botulinum toxin (BoNT) has been used for the treatment of a variety of neurologic, medical and cosmetic conditions. Two serotypes, type A (BoNT-A) and type B (BoNT-B), are currently in clinical use. While considered safe and effective, their use has been rarely complicated by the development of antibodies that reduce or negate their therapeutic effect. The presence of antibodies has been attributed to shorter dosing intervals (and booster injections), higher doses per injection cycle, and higher amounts of antigenic protein. Other factors contributing to the immunogenicity of BoNT include properties of each serotype, such as formulation, manufacturing, and storage of the toxin. Some newer formulations with purified core neurotoxin devoid of accessory proteins may have lower overall immunogenicity. Several assays are available for the detection of antibodies, including both structural assays such as ELISA and mouse-based bioassays, but there is no consistent correlation between these antibodies and clinical response. Prevention and treatment of antibody-associated non-responsiveness is challenging and primarily involves the use of less immunogenic formulations of BoNT, waiting for the spontaneous disappearance of the neutralizing antibody, and switching to an immunologically alternate type of BoNT.

Detection and management of secondary non-responsiveness



Bellows S, Jankovic J. Toxins 2019;11(9)

Right UBI – patient responds

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BoNT products

Products	Manufacturer Distributor	Country
OnabotulinumtoxinA (Botox, Vistabel, Vistabex, Botox Cosmetic)	Allergan/Abbvie	USA
AbobotulinumtoxinA (Dysport, Reloxin, Azzalure)	Ipsen	France
IncobotulinumtoxinA (Xeomin, Bacouture)	Merz	Germany
RimabotulinumtoxinB (Myobloc, Neurobloc, Nerbloc)	US World Meds	USA
Neuronox, Botulif, Cunox, KbtxA, Meditoxin, Neuramis, Siax, MT 10107, MT 10109, Meditoxin, Medy-Tox	Medytox	Korea
Prosigne, LanbotulinumtoxinA, BTX-A, CBTX-A, Hengli, Lantox, Lanzox	Lanzhou Biological Products	China
LetibotulinumtoxinA (Botulax)	Hugel	Korea
PurTox	Mentor Corporation	USA
Nabota, DWP-450, Evosyal, Jeuveau	Daewoong Pharmaceutical	Korea
A2NTX	Shionogi Pharma	Japan
DaxibotulinumtoxinA (RTR002)	Revance Therapeutics	USA
PrabotulinumtoxinA (ABP-450)	AEON BioPharma	USA

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DaxibotulinumtoxinA

- **RTP004, the positively-charged stabilizing excipient peptide, attaches to the negatively charged core neurotoxin in the DAXI formulation, and increases the affinity of the daxibotulinumtoxinA for neuronal membranes, which enhances localization of DAXI at the presynaptic terminal and may, therefore, facilitate increased internalization of the botulinum toxin molecule.**
- **Purified 150 kDa BoNTA without accessory proteins.**
- **Has been found to have prolonged duration of effect in reducing glabellar lines.**
- **On 9/8/22 *DAXXIFY*™ *a*pproved by the FDA for the treatment of glabellar lines.**
- **On 8/14/23 *DAXXIFY*™ *a*pproved by the FDA for the treatment of cervical dystonia.**
- **A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Trial to Evaluate the Efficacy and Safety of a Single Treatment of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-1) – results published in 2024.**

Injectable DaxibotulinumtoxinA in Cervical Dystonia:
A Phase 2 Dose-Escalation Multicenter Study

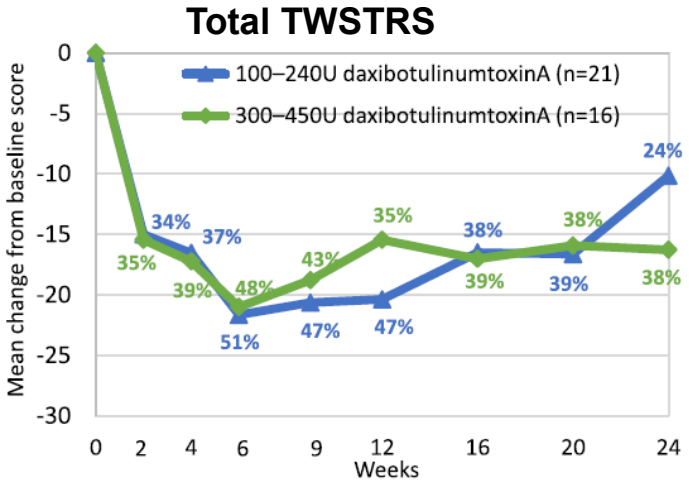
Jankovic et al. Mov Disord Clin Practice 2018;5:273–82

- **DaxibotulinumtoxinA is a purified 150 kDa BoNT-A (RTT150) that is devoid of accessory proteins and formulated with a proprietary stabilizing excipient peptide (RTP004) in a lyophilized powder.**
- **Formulated without human serum albumin daxibotulinumtoxinA is room temperature stable prior to reconstitution.**
- **Preliminary assessments suggest that injectable daxibotulinumtoxinA at doses up to 450U is well tolerated and may offer prolonged efficacy in the treatment of cervical dystonia.**
- **33/37 enrollees completed the trial.**
- **The median duration of response (time until >20% of the improvement in TWSTRS-Total score achieved at week 4 was no longer retained or retreatment was needed) was 25.3 weeks (95% CI, 20.14–26.14 weeks).**
- **The most common treatment related adverse events were dysphagia (14%) and injection site erythema (8%).**

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Injectable DaxibotulinumtoxinA in Cervical Dystonia:
A Phase 2 Dose-Escalation Multicenter Study

Jankovic et al. Mov Disord Clin Practice 2018;5:273–82



- 33/37 (89%) completed the trial
- Mean reduction in Total TWSTRS 16.8 (38%) at week 4, 21.3 (50%) at week 6, and 12.8 (30%) at week 24
- AEs: Mild dysphagia (14%), weakness (5%), neck pain 3%

DaxibotulinumtoxinA (RT002)

- Purified 150 kDa BoNTA without accessory proteins
- Novel excipient - may reduce spread of toxin, extend the half-life

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RESEARCH ARTICLE OPEN ACCESS

Efficacy and Safety of DaxibotulinumtoxinA for Injection in Cervical Dystonia

ASPEN-1 Phase 3 Randomized Controlled Trial

Cynthia L. Comella, MD, Joseph Jankovic, MD, Robert A. Hauser, MD, Atul T. Patel, MD, Marta D. Banach, MD, PhD, Edvard Ehler, MD, Domenico Vitarella, PhD, Roman G. Rubio, PhD, and Todd M. Gross, PhD, on behalf of the ASPEN-1 Study Group

Correspondence
Dr. Comella
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Neurology® 2024;102:e208091. doi:10.1212/WNL.0000000000208091

Abstract

Background and Objectives

ASPEN-1 was a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, duration of response, and safety of 2 doses of DaxibotulinumtoxinA for Injection (DAXI), a novel botulinum toxin type A formulation in participants with cervical dystonia (CD).

Methods

Adults (aged 18–80 years) with moderate-to-severe CD (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] total score ≥20) were enrolled at 60 sites across 9 countries in Europe and North America. Participants were randomized (3:3:1) to single-dose intramuscular DAXI 125U, 250U, or placebo and followed for up to 36 weeks after injection. The primary end point was change from baseline in TWSTRS total score averaged across weeks 4 and 6. Key secondary end points included duration of effect, Clinical and Patient Global Impression of Change (CGIC, PGIC), TWSTRS subscale scores, and safety. Multiplicity-adjusted intent-to-treat hypothesis tests with multiple imputation were performed using ANCOVA and Cochran-Mantel-Haenszel analyses.

Results

Of 444 individuals screened, 301 were randomized to DAXI 125U (n = 125) or 250U (n = 130) or placebo (n = 46). DAXI 125U and 250U significantly improved the mean TWSTRS total score vs placebo (least squares mean [standard error] difference vs placebo: DAXI 125U, −8.5 [1.93], $p < 0.0001$; DAXI 250U, −6.6 [1.92], $p = 0.0006$). The median duration of effect (time from treatment until loss of ≥80% of the peak improvement in average TWSTRS total score achieved at weeks 4 and 6) was 24.0 (95% confidence interval 20.3–29.1) weeks with DAXI 125U and 20.3 (16.7–24.0) weeks with DAXI 250U. Significant improvements were also observed with DAXI in CGIC and PGIC responder rates and TWSTRS subscales. Treatment-related treatment-emergent adverse events (TEAEs) were reported by 29.6% of participants with DAXI 125U, 23.8% with DAXI 250U, and 17.4% with placebo, with injection site pain being the most common overall. The most frequently reported treatment-related TEAEs of interest in DAXI 125U, DAXI 250U, and placebo, respectively, were muscular weakness (4.8%, 2.3%, 0%), musculoskeletal pain (2.4%, 3.1%, 0%), and dysphagia (1.6%, 3.8%, 0%).

Discussion

This study demonstrated that DAXI, at doses of 125U and 250U, is an effective, safe, long-acting, and well-tolerated treatment for CD.

MORE ONLINE

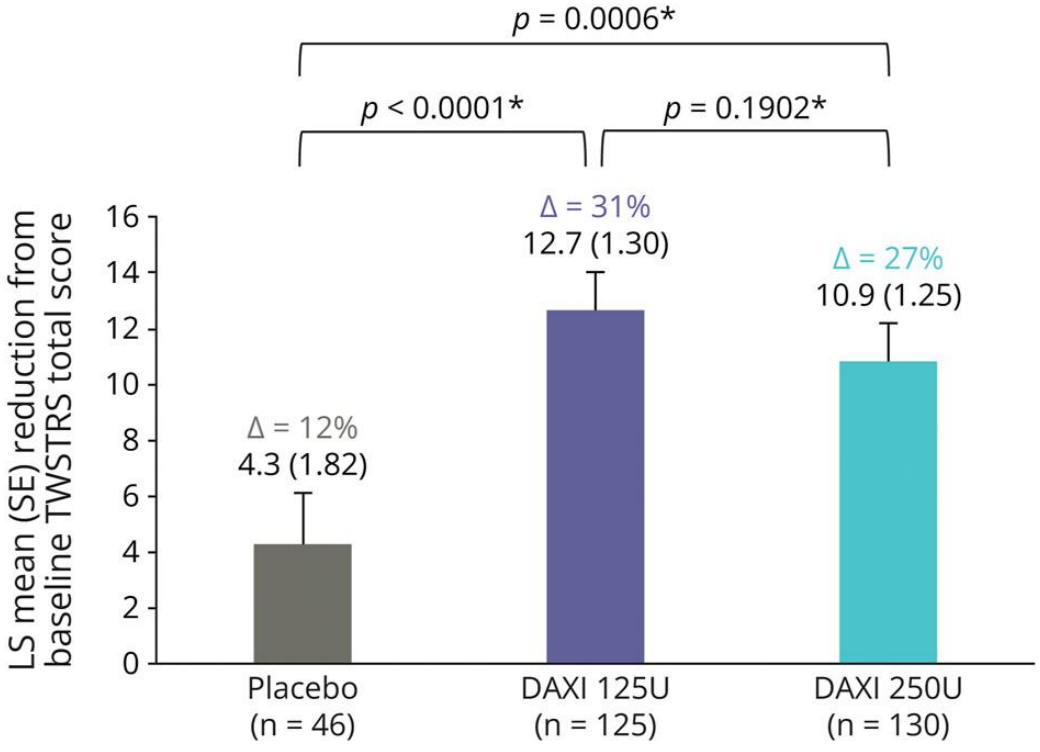
Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Efficacy and Safety of DaxibotulinumtoxinA for Injection in Cervical Dystonia: ASPEN-1 Phase 3 Randomized Controlled Trial.

Comella et al. Neurology 2024;102:e208091

- **Of 444 individuals screened, 301 were randomized to DAXI 125U (n = 125) or 250U (n = 130) or placebo (n = 46).**
- **DAXI 125U and 250U significantly improved the mean TWSTRS total score vs placebo: DAXI 125U, -8.5, $p < 0.0001$; DAXI 250U, -6.6, $p = 0.0006$). The median duration of effect was 24.0 weeks with DAXI 125U and 20.3 weeks with DAXI 250U. Significant improvements were also observed in CGIC and PGIC responder rates and TWSTRS subscales.**
- **Treatment-related adverse events were reported by 29.6% of participants with DAXI 125U, 23.8% with DAXI 250U, and 17.4% with placebo, and included injection site pain, muscular weakness, musculoskeletal pain, and dysphagia (all <5%).**
- **Conclusion: This study demonstrated that DAXI, at doses of 125U and 250U, is an effective, safe, long-acting, and well-tolerated treatment for CD.**

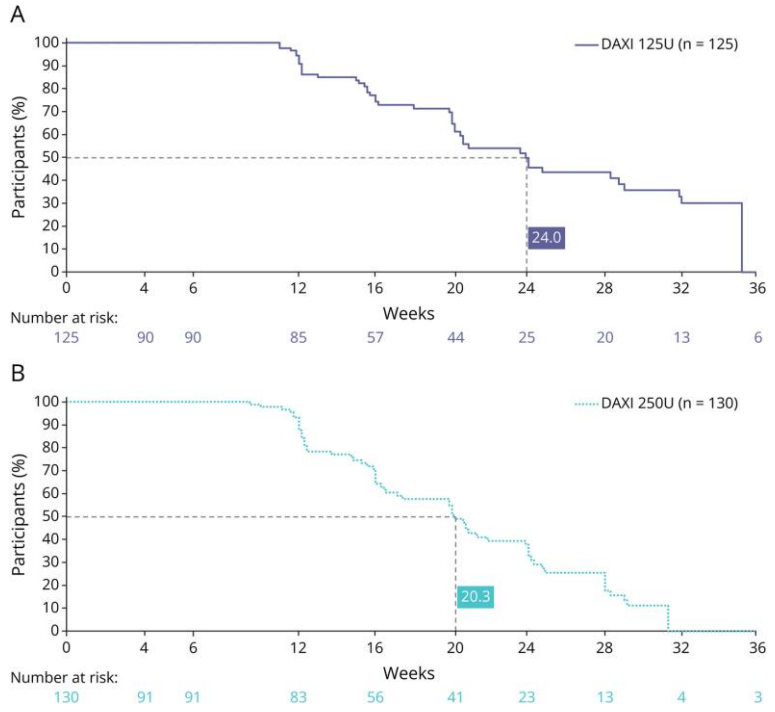
Change From Baseline in TWSTRS Total Score Averaged Across Weeks 4 and 6



Comella CL, Jankovic J, Hauser RA et al. Neurology 2024;102:e208091

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Time to Loss of ≥80% of Peak Treatment Effect (Defined as TWSTRS Total Score Averaged Across Weeks 4 and 6) for (A) DAXI 125U and (B) DAXI 250U



Comella CL, Jankovic J, Hauser RA et al. Neurology 2024;102:e208091

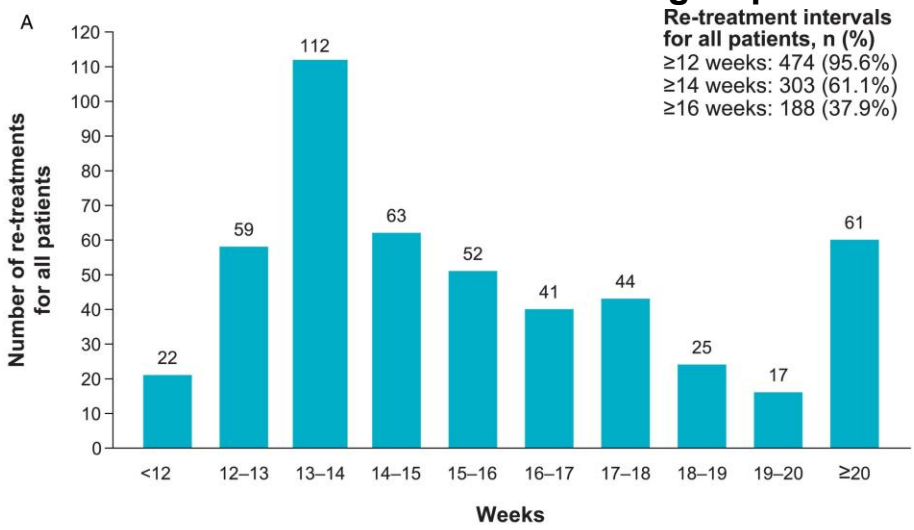
73

DaxibotulinumtoxinA for Injection in Adults with Cervical Dystonia:

Clinical Insights from a Real-World Early Experience Program.

Bahroo et al. Mov Disord Clin Pract 2026;13:1644-52

Time to re-treatment with DAXI among all patients



The ratio of DAXI dose to prior BoNT dose was approximately 1.1:1 at initiation and 1.4:1 at Cycle 3. The mean (SD) time to re-treatment across all DAXI cycles was 16.1 (5.6) weeks. The most common adverse events were muscle weakness (2.4%), injection pain (1.4%), and dysphagia (0.3%).

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PrabotulinumtoxinA (ABP-450)

- PrabotulinumtoxinA is a new botulinum toxin type A preparation produced by Clostridium botulinum first developed by Daewoong Pharmaceutical Co., Ltd. of Seoul, South Korea. It was licensed to Evolus, Inc. of Newport Beach, CA, and is marketed by Aeon as Jeuveau in the United States.
- PrabotulinumtoxinA contains a 900 kDa botulinum toxin type-A complex produced by the bacterium Clostridium botulinum. The active part of the botulinum toxin is the 150 kDa component, and the remaining 750 kDa of the complex is made up of accessory proteins
- On 9/23/22 AEON Biopharma reported positive results from Phase 2 Clinical Trial of ABP-450 (prabotulinumtoxinA) in Cervical Dystonia.
  – All three dosing arms demonstrated a median duration of effect for ≥20 weeks

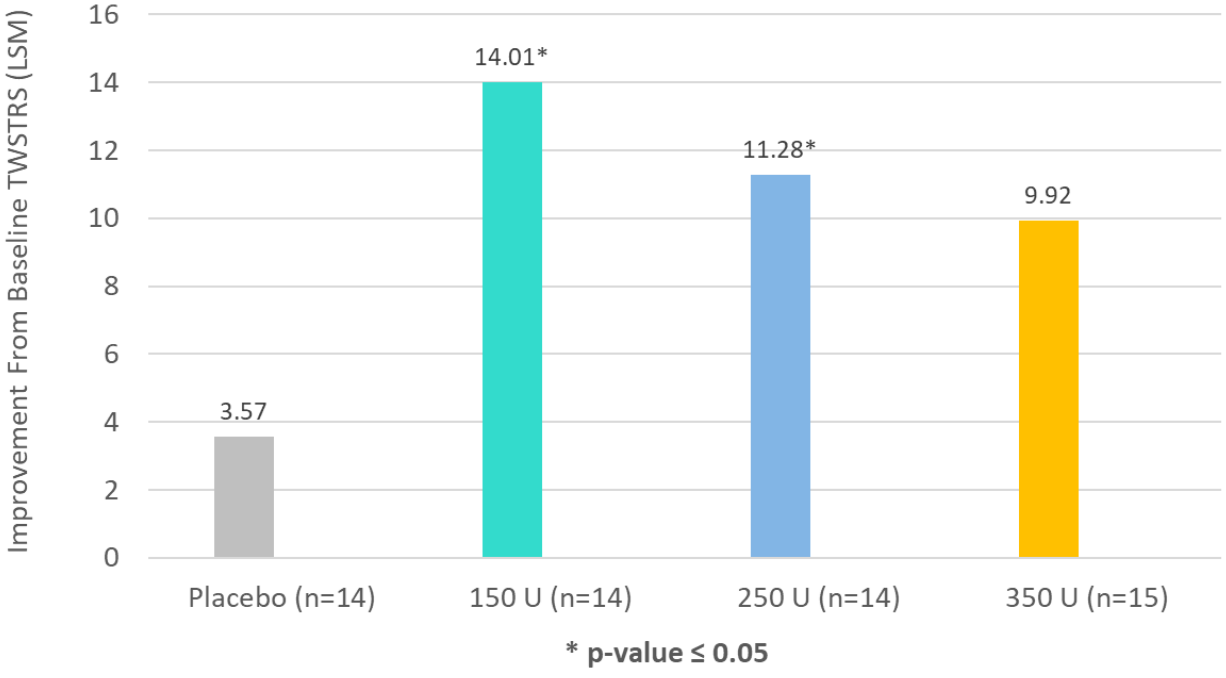
A Phase 2, Double-blinded, Multi-Center Trial to Evaluate the Efficacy and Safety of Repeat Treatments of ABP-450 (PrabotulinumtoxinA) in Adults with Isolated Cervical Dystonia.

Jankovic J, Oh C, Liu Y, Comella C.
Presented at the International Congress of Parkinson and Movement Disorders, Copenhagen, Denmark, 8/29/23

- **Of the 70 subjects screened, 57 were included in the efficacy analysis.**
- **Treatment effect (vs. placebo) based on mean change from baseline in TWSTRS total score at week 4 was -10.44 (p=0.0070) for 150U, -7.71 (p=0.0406) for 250U, and -6.35 (p=0.0864) for 350U.**
- **Treatment-related adverse effects (TEAE) were reported in 16 subjects (36%), with the most frequent being dysphagia (11.1%), muscular weakness (6.7%), and headache (4.4 %).**
- **Conclusion: ABP-450 at doses of 150U and 250U demonstrated statistically significant and clinically meaningful efficacy. ABP-450 appeared to be generally safe and well tolerated.**

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Primary Efficacy Endpoint: Mean Improvement from Baseline TWSTRS–Total Score at Week 4



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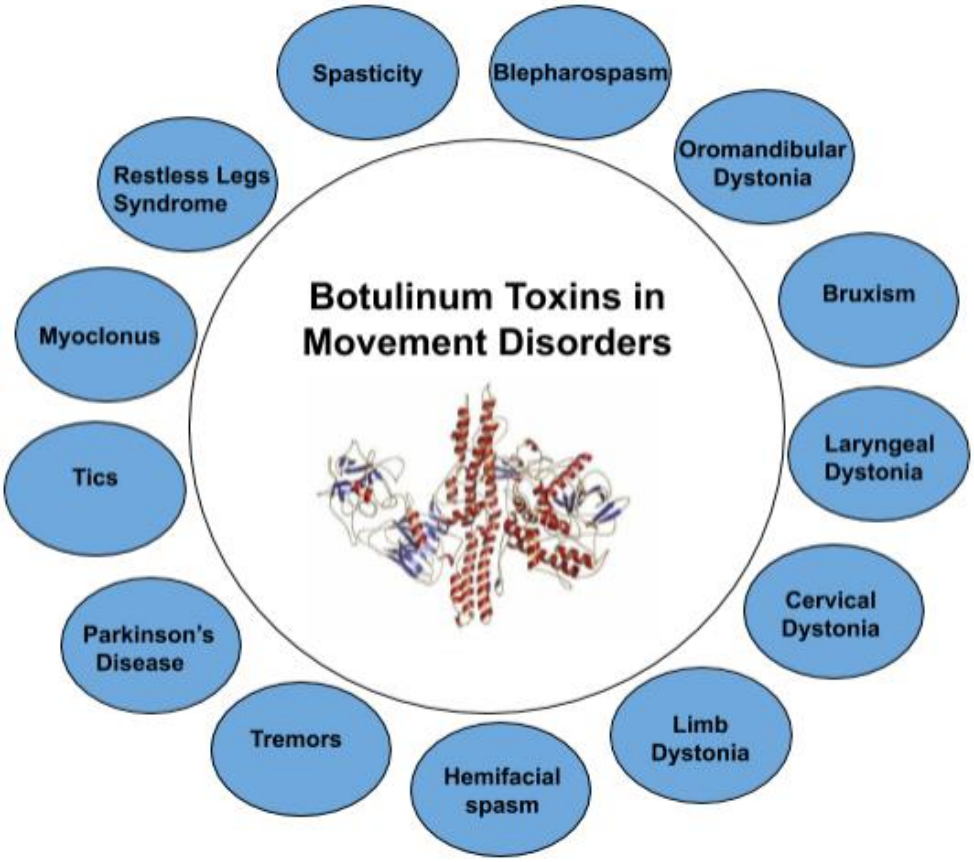
Botulinum Neurotoxin Injections in Childhood Opisthotonus.

Hull M, Parnes M, Jankovic J. Toxins 2021;13:137

2 y/o F with global developmental delay, epilepsy, and dystonic storm
Pre- and Post-BoNT injection

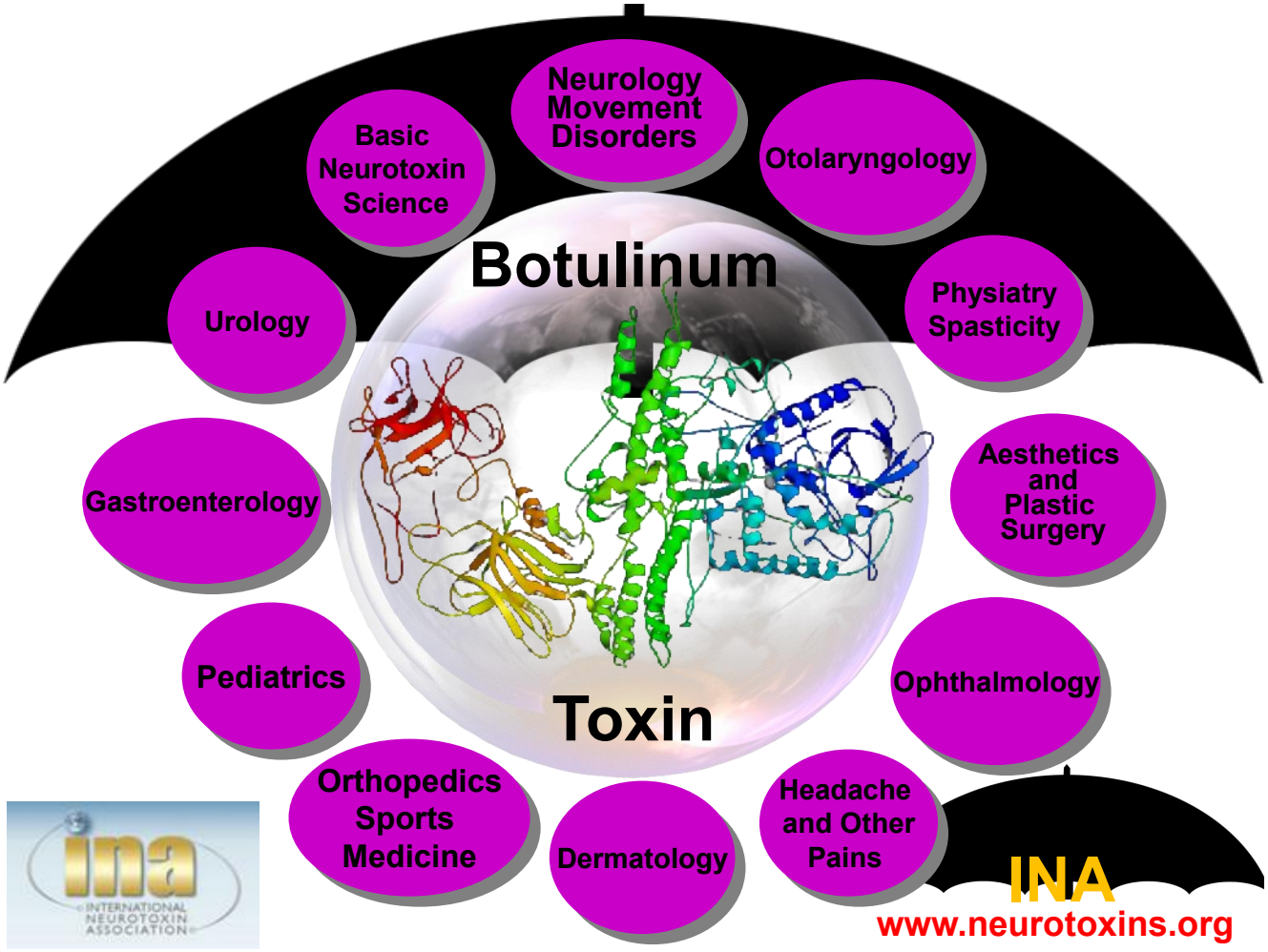


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Anandan C, Jankovic J. Toxins 2021;13:42

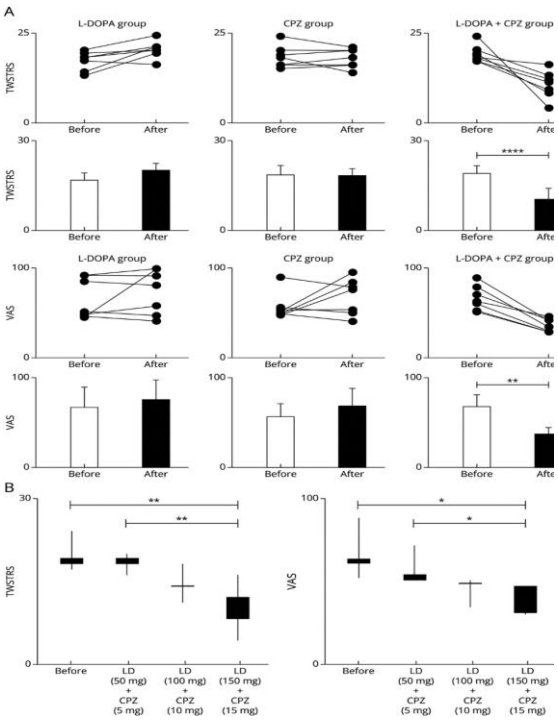
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Neurology
Movement
Disorders
Basic
Neurotoxin
Science
Otolaryngology
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Therapeutic Effects of Dual Dopaminergic Modulation With L-DOPA and Chlorpromazine on Cervical Dystonia.

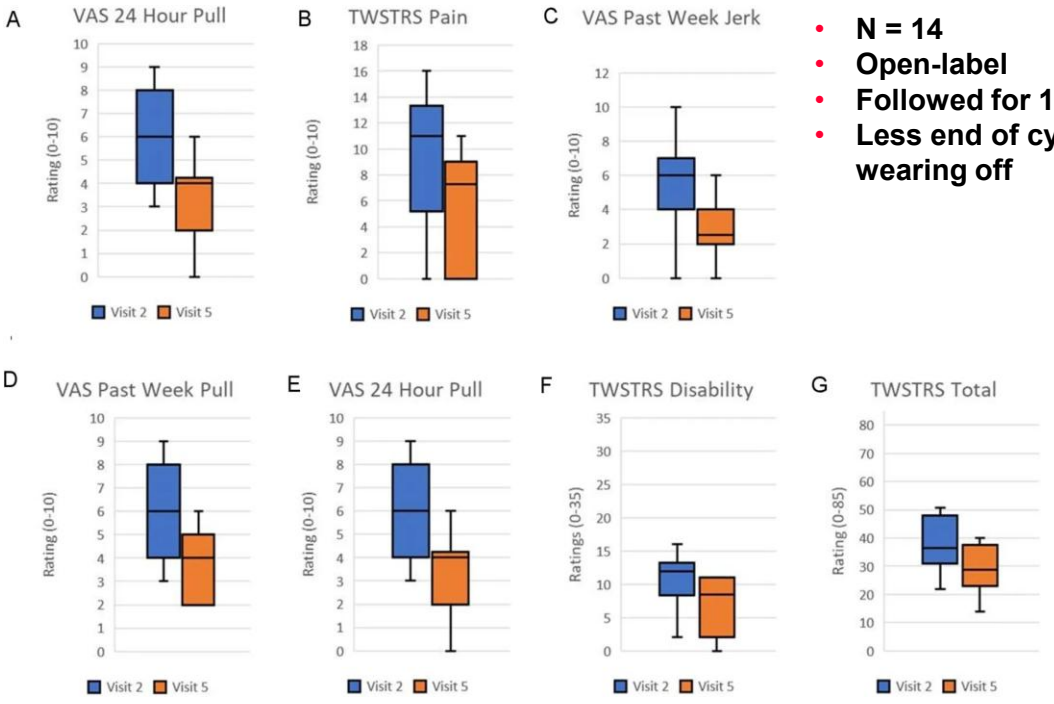
- **Impairments of activity balance between dopamine D1 and D2-like receptors in the striosome-matrix system may lead to dystonia.**
- **21 patients with CD who responded poorly to botulinum toxin treatment.**
- **Significant decrease in the TWSTRS and VAS with combination of L-DOPA-carbidopa (150 mg/d) and CPZ (15 mg/d), $p < 0.001$.**



Matsumoto et al. Neurol Clin Pract 2024;14:e200254

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Valbenazine appears to prolong the effects of BoNT in patients with cervical dystonia.



- **N = 14**
- **Open-label**
- **Followed for 16 wks**
- **Less end of cycle wearing off**

Aziz et al. Dystonia 2025;4:13923

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Experimental therapeutics of dystonia

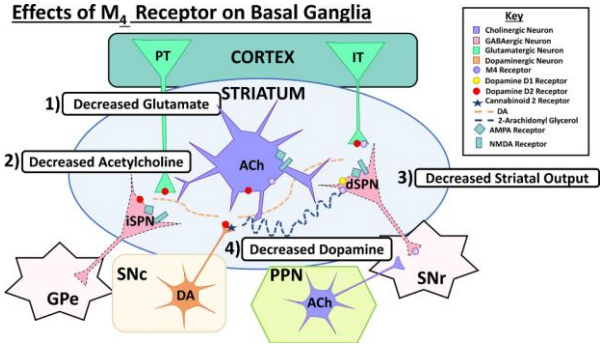
- **Parampanel (AMPA-selective glutamate receptor antagonist)**
  Fox et al. 2021, Open-label, N=25 (CD) **- negative**
- **Cannabinoid receptor agonists**
  Fox et al. 2002 RDBPC, Nabilon, N=15 **- negative**
  Zadikoff et al. 2011 RDBPC, Dronabinol, N= 9 (CD) **- negative**
- **Dipraglurant (mGluR5 negative allosteric modulator) - negative**
- Kilic-Berkmen et al. Mov Disord 2024;39:738-45

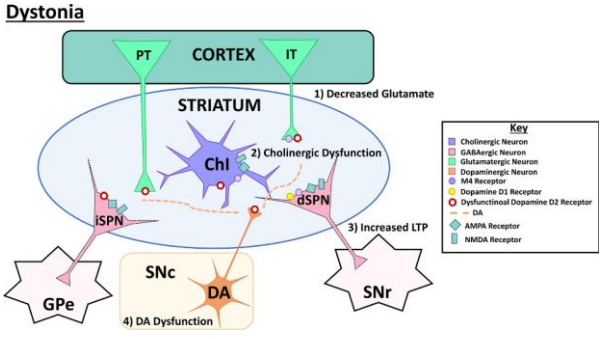
- **Dopamine receptor agonists**
- **NMDA receptor antagonists**
- **Adenosine A2A receptor antagonists**
- **AMPA antagonists**
- **Ampicillin - NCT01433757**
- **Ritonavir - HIV protease inhibitor**
- **Selective M_4 muscarinic acetylcholine receptor antagonists**

*** Many animal studies show promising results, but …**

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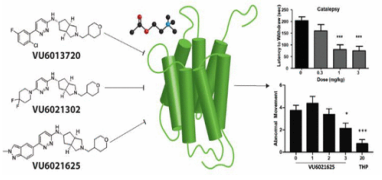
Muscarinic Acetylcholine Receptor (M_4) Antagonists in the Treatment of Dystonia





- M_4 receptors serve as autoreceptors on striatal cholinergic interneurons
- M_4 receptors, located on terminals of corticostriatal glutamate projections, inhibit glutamate release
- M_4 receptor counter DA signaling

- Increased striatal ACh release
- Increased corticostriatal glutamate release
- M_4 antagonists may be effective in the treatment of dystonia



Downs et al. Neurobiol Dis 2022;168:105699
Chambers et al. Biochem Soc Trans 2023; 51:691-702

VIM0423

- **VIM0423, developed by Vima Therapeutics, Inc., is designed to target muscarinic cholinergic receptors in the brain with improved pharmacology, efficacy, and safety.**
- **Isomer of trihexyphenidyl (extended release 1/day) plus peripheral muscarinic agonist, bethanechol.**
- **VIM0423 has been granted Fast Track designation by the FDA.**
- **Potential first-in-class oral medicine for isolated dystonia currently being studied in a Phase 1 clinical trial; Phase 2 planned for 2026.**
- **A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of VIM0423 in Individuals With Isolated Dystonia (Stride Dystonia).**
  - **ClinicalTrials.gov ID NCT07304089**
  - **Sponsor: Vima Therapeutics**
  - **https://www.stridedystonia.com**

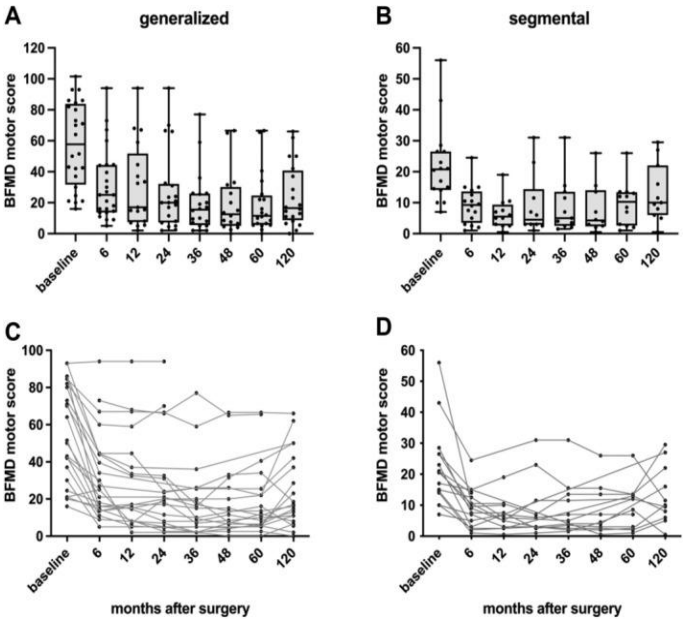
MTR-601

- MTR-601, developed by Motric Bio, Inc (Motric), is a novel, orally administered small molecule – prevents binding of myosin-2 to actin.
- Inhibitor of myosin-2 "fast" isoforms that selectively stabilizes the actin unbound conformation of myosin-2 isoforms that have a leucine at position 476 instead of a phenylalanine; selectivity spares "slow" isoforms found in cardiac and smooth muscle and enables the efficient nervous system-independent relaxation of abnormally contracting muscles.
- MTR-601 was evaluated in a randomized, double-blind, placebo-controlled, Phase 1, first-in-human clinical trial, and was found to be safe and well tolerated at all dose levels in single and multiple dosing.
- Adverse events included mild visual disturbances (potentially related to extra-ocular muscle weakness), dizziness and drowsiness.
- In a preclinical model, MTR-601 was also shown to improve gait function in spastic cerebral palsy.

Long-Term Outcomes on Pallidal Neurostimulation for Dystonia: A Controlled, Prospective 10-Year Follow-Up.

Krause et al. Mov Disord 2025;40:1098-111

- 31 patients (12 female), aged 23-72 years, completed the 10-year study extension.
- BFMDRS motor scores decreased by 25.3 ± 5.2 points at 10 years (P < 0.0001; 56% improvement).
- 27 responders (≥25% improvement; mean improvement 65.2 ± 21.4%) and 13 non-responders.
- Sustained improvements were seen in disability, mood, and anxiety scores. Cognition remained stable.

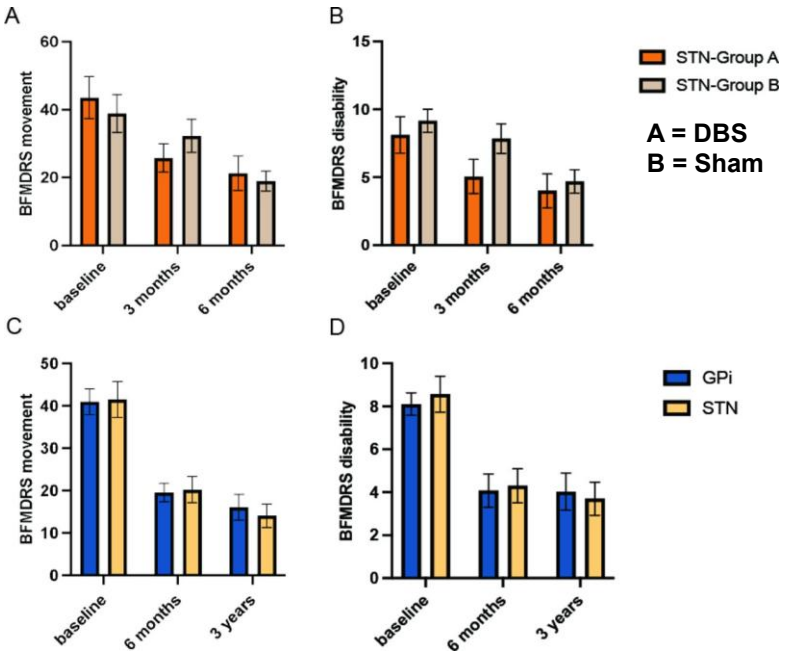


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Subthalamic deep brain stimulation in isolated generalised or segmental dystonia (RELAX Study): a multicentre, randomised, double-blind, controlled trial.

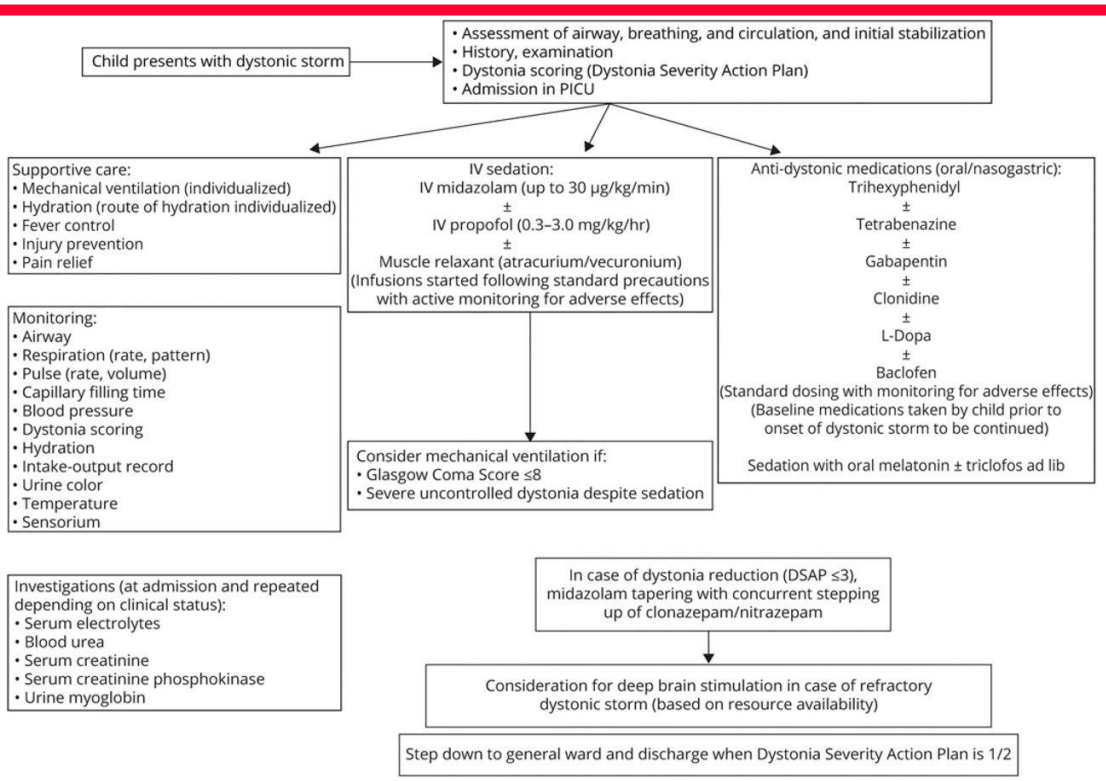
Wang et al. J Neurol Neurosurg Psychiatry 2025;96:1077-88

- **72 patients with isolated dystonia**
- **STN DBS improved dystonia > sham DBS**
- **Both STN-DBS and GPi-DBS produced similar therapeutic effects**



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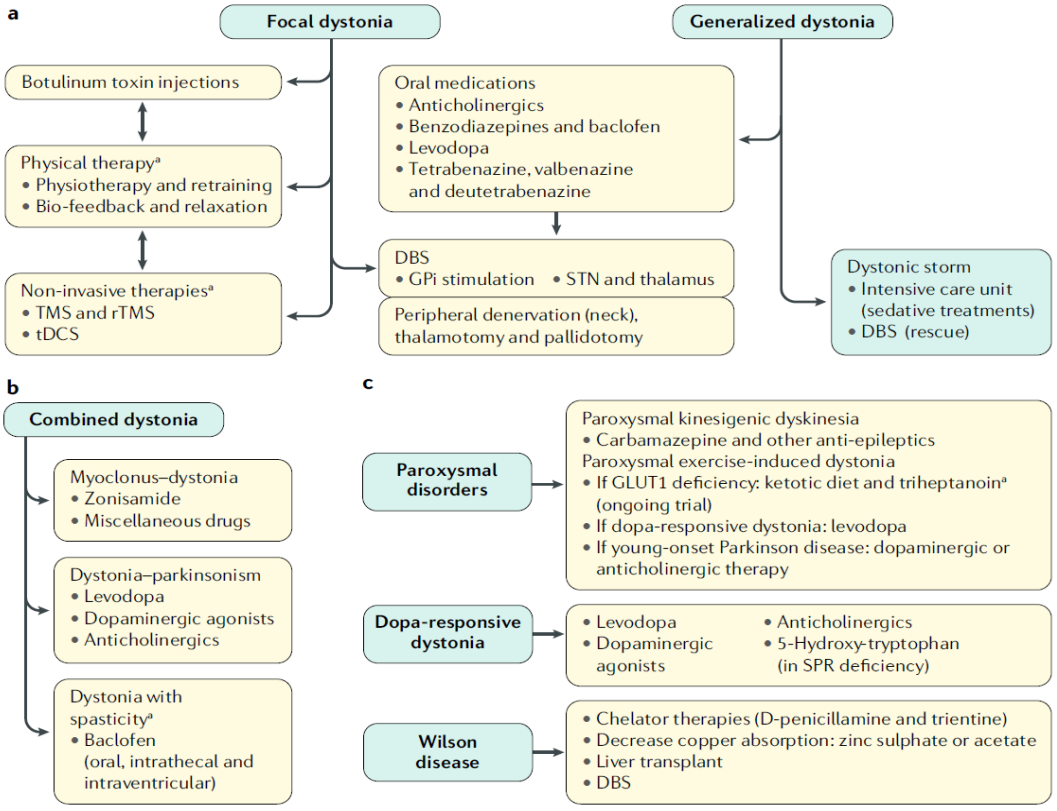
Algorithm for Dystonic Storm Management



Goswami et al. Neurol Clin Pract 2021;11:e645-e653
Also - Lumsden et al. Parkinsonism Relat Disord 2023;112:105438;
Vogt et al. Mov Disord 2024;39:1435-45

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Treatment algorithm for dystonia



Balint B, Mencacci NE, Valente EM, Pisani A, Rothwell J, Jankovic J, Vidailhet M, Bhatia KP. Dystonia. Nat Rev Dis Primers 2018;4:25

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DYT1 Dystonia
6 y/o Hispanic girl with rapidly progressive dystonia



Courtesy Dr. Stocco

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