Cervical Dystonia

9th Annual Cleveland Clinic Comprehensive Neurotoxin Course for Neurological Conditions

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Cervical Dystonia

- Abnormal head/neck postures and movements, shoulder elevation, muscle contractions and hypertrophy
- 10/100,000 people; female/male 2:1; peak age at onset 40–50 years
- Natural history: typically progresses for the first 5 years
  - 1/3 spread beyond the neck within 5 years
  - 1/3 experience transient remission within 5 years
- Tremor: 1. Dystonic tremor (irregular, slow, null point); 2. ET-like tremor, 25% have postural tremor in their hands (ET?)
- Gait and balance problems – partly related to reduced ROM
- >10% have dysphagia (>20% have peristaltic abnormality)
- NMS: 75% neck pain; also sleep impairment, depression, anxiety, etc
- Alleviating maneuvers (sensory tricks; geste antagoniste), compensation/overcompensation
- 1/3 have family history of dystonia or tremor
- Other causes: orthopedic, congenital muscular torticollis, posterior fossa or cervical cord tumors, neck or pharyngeal abscess, neck injury
- ICD-10: G24.3, M43.6 (torticollis)

Examination of Patients with Cervical Dystonia
Critical for selection of appropriate target muscles

- Examine postures and movements in a 3D space
  - At rest in a sitting/lying position (also with eyes closed)
  - Using activation and deactivation tasks (walking, standing, reading, writing, arms held outstretched, finger-nose)
- Determine in which direction the head/neck moves spontaneously and easily, and in which direction there is resistance/reduced range of motion (contracture)
- Differentiate between primary agonist and secondary antagonist (compensatory) contractions (overcompensation?)
- Describe the most abnormal posture(s) (torticollis, laterocollis, retrocollis, anterocollis, sagittal shift, shoulder elevation, scoliosis)
- Is there an alleviating maneuver (geste antagoniste/sensory trick)?
- Head tremor (dystonic, essential); find the “null point”
- Ask about pain, tenderness on palpation
- Observe/palpate/measure muscle hypertrophy
- Perform TWSTRS
- Videotape before initial injection

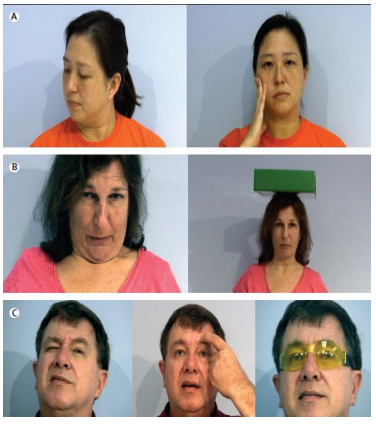
Sensory aspects of movement disorders

Neepa Patel, Joseph Jankovic, Mark Hallett

Lancet Neurol 2014; 13: 100–12

Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, USA (N Patel MD, Prof J Jankovic MD); and Human Motor Control Section, NINDS, National Institutes of Health, Bethesda, MD, USA (Prof M Hallett MD)

Movement disorders, which include disorders such as Parkinson's disease, dystonia, Tourette's syndrome, restless legs syndrome, and akathisia, have traditionally been considered to be disorders of impaired motor control resulting predominantly from dysfunction of the basal ganglia. This notion has been revised largely because of increasing recognition of associated behavioural, psychiatric, autonomic, and other non-motor symptoms. The sensory aspects of movement disorders include intrinsic sensory abnormalities and the effects of external sensory input on the underlying motor abnormality. The basal ganglia, cerebellum, thalamus, and their connections, coupled with altered sensory input, seem to play a key part in abnormal sensorimotor integration. However, more investigation into the phenomenology and physiological basis of sensory abnormalities, and about the role of the basal ganglia, cerebellum, and related structures in somatosensory processing, and its effect on motor control, is needed.



Alleviating maneuvers

Alleviating maneuvers (sensory tricks) in cervical dystonia.

Patel et al (Dystonia Coalition). J Neurol Neurosurg Psychiatry 2014;85:882-4

- **Alleviating maneuvers, also referred to as sensory tricks or geste antagoniste, are used by patients to correct their dystonic posture or stop the abnormal movement.**
- **Alleviating maneuvers – a more appropriate term because "sensory trick" suggests that only sensory input is required, and the word "trick" implies that it is "fake". Furthermore, the term 'sensory trick' has been wrongly interpreted as implying psychological origin of dystonia.**
- **Of 154 people studied, 138 (89.6%) used alleviating maneuvers, of which 60 (43.4%) reported partial improvement, 55 (39.8%) marked improvement, and 4 (0.03%) no effect on dystonic posture.**
- **Of the patients using alleviating maneuvers, 125 (90.5%) used light touch and 13 (9.4%) used forced touch.**
- **The presence or location of alleviating maneuvers did not correlate with the severity of the dystonia.**

REVIEW

Medical Treatment of Dystonia

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Mov Disord 2013;28:1001-12

ABSTRACT: Medications such as anticholinergic drugs, dopamine modulators, baclofen, muscle relaxants, and other pharmacologic agents have been used for a long time to treat dystonia, but the introduction of botulinum toxin and deep brain stimulation clearly revolutionized the symptomatic treatment of this neurological movement disorder. Therapy of dystonia can be divided into the following categories: (1) physical, supportive, and ancillary therapy; (2) pharmacologic treatment; (3) chemodenervation with botulinum toxin; and (4) peripheral and central surgery (deep brain stimulation). Except in some cases of secondary dystonia, pathogenesis-targeted or disease-modifying therapy is currently not available. This review focuses on evidence-based medical treatment of dystonia, highlighting recent advances, with emphasis on individualized approach. © 2013 *Movement* Disorder Society

Key Words: dystonia; botulinum toxin; baclofen; trihexyphenidyl; tetrabenazine

Thenganatt MA, Jankovic J. Treatment of dystonia. Neurotherapeutics. 2014;11:139-52

Guiding Principles in the Treatment of Dystonia

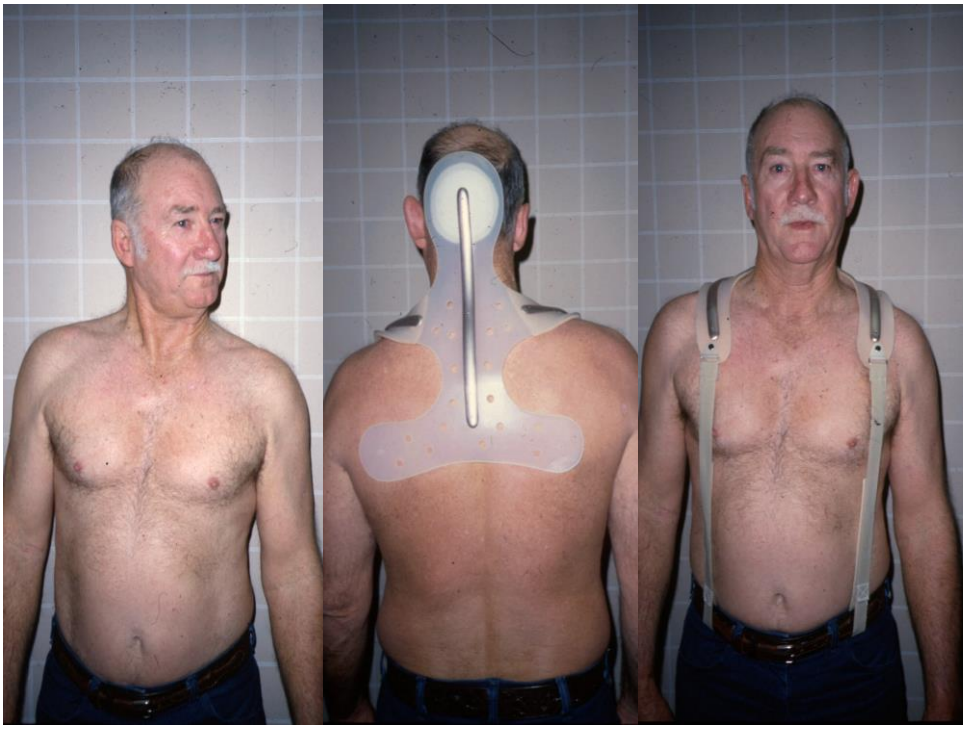
- **Identify a specifically treatable cause (e.g. Wilson's disease, drugs, structural lesions, metabolic abnormalities)**
- **Educate patient and family (genetic counseling)**
- **Address co-morbidities (depression, orthopedic complications)**
- **Explain that therapy for dystonia is symptomatic not protective**
- **Select treatment according to severity, age, type, and distribution**
- **Encourage patients to discover alleviating maneuvers (sensory tricks)**
- **Range of motion exercises to prevent contractures**
- **L-Dopa in childhood- and young-onset dystonia**
- **Many 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**

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**



Therapy of Dystonia

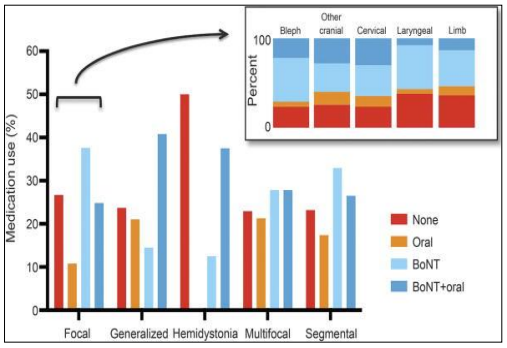
- **Levodopa**
- **Anticholinergics**
- **Baclofen: oral, intrathecal**
- **VMAT2 inhibitors** (tetrabenazine, deutetrabenazine, valbenazine)
- **Anticonvulsants** (carbamazepine, pregabalin, levetiracetam, zonisamide)
- **Perampanel** (selective AMPA receptor antagonist)
- **Sodium oxybate** (salt of gamma-hydroxybutyrate)
- **Zolpidem** (imidazopyridine agonist that binds to $GABA_A$ receptors)
- **Clozapine** (inhibitor of D2, 5-HT2, alpha-adrenergic, and cholinergic receptors)
- **Muscle relaxants:**
  - **Benzodiazepines** (clonazepam, lorazepam, diazepam, alprazolam)
  - **Other relaxants** (tizanidine, cyclobenzaprine, metaxalone, carisoprodol, methocarbamol, orphenadrine)
- **Botulinum toxin**
- **Deep brain stimulation**

Dystonia treatment:

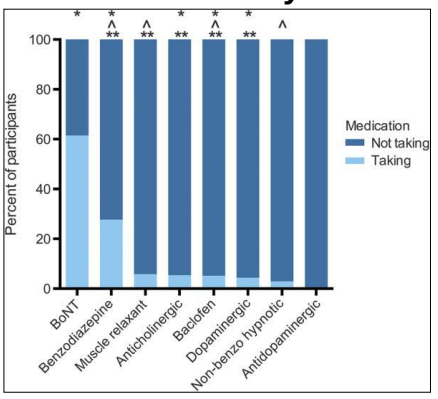
Patterns of medication use in an international cohort.

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

Medication use by dystonia type and subtype



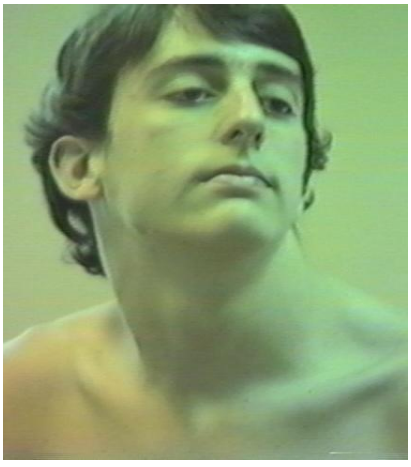
Medication use by class



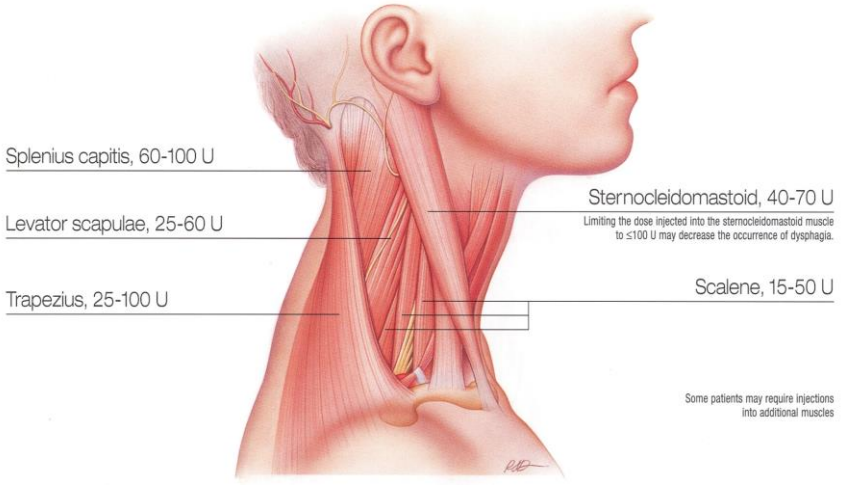
- **2,026 participants with isolated dystonia at 37 Dystonia Coalition sites**
  - **Focal dystonia (76.4%; CD - 60.9%), segmental dystonia (16.4%), generalized dystonia (3.8%), multifocal dystonia (3%), hemidystonia (0.4%)**
- **1,488 (73%) used medications for dystonia; 61% of the total sample used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

Botulinum Toxin in Cervical Dystonia

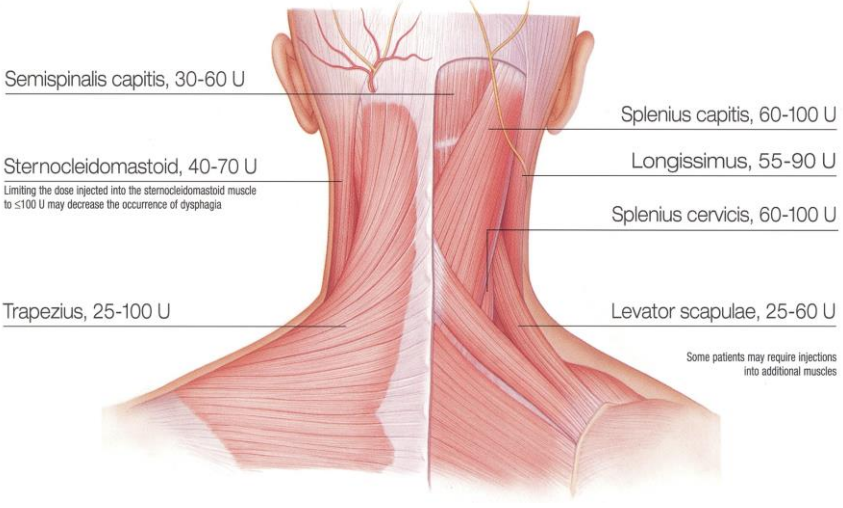
Before



After



Dosages in BoNT-A (OnabotulinumtoxinA)



Dosages in BoNT-A (OnabotulinumtoxinA)

Cervical Dystonia

- Muscles of neck are complex (> 30 pairs of opposing muscles)
  - **Torticollis** — contralateral SCM, ipsilateral splenius
  - **Laterocollis** — ipsilateral splenius, longissimus, scalene, SCM
  - **Retrocollis** — bilateral splenius, longissimus, upper trapezius
  - **Anterocollis** — submental complex, scalene, SCM

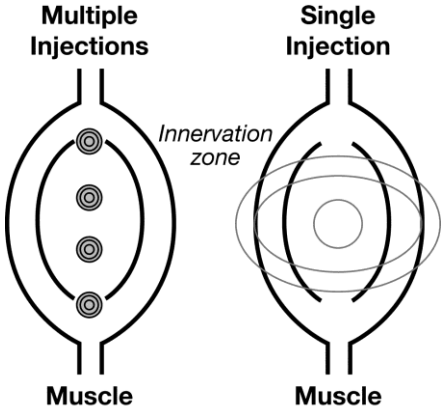
Recommended Dosing of BoNT in CD

Muscle	BoNT-A (OnaA; IncoA)	BoNT-A (AboA)	BoNT-B (RimaB)
Trapezius	35 – 100	100 – 250	1,500 – 5,000
Sternocleidomastoid	25 – 75	70 – 200	2,000 – 3,500
Splenius capitis	35 – 75	100 – 200	2,000 – 3,500
Levator scapulae	25 – 50	70 – 125	1,250 – 2,500
Scalene complex	25 – 60	70 – 150	1,250 – 3,000

Diffusion, spread, and migration of botulinum toxin

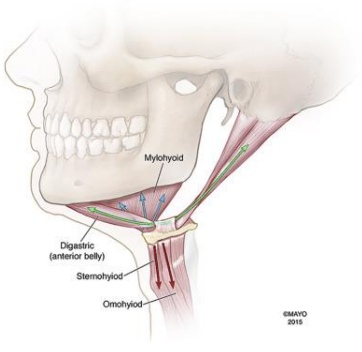
Ramirez-Castaneda J, Jankovic J, Comella C, Dashtipour K, Fernandez HH, Mari Z. Mov Disord 2013;28:1775-83

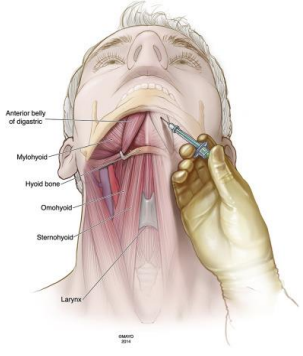
Most of the local and remote complications of BoNT injections are due to unwanted spread or diffusion of the toxin's biologic activity into adjacent and distal muscles.



Hyoid muscle dystonia:
A distinct focal dystonia syndrome.

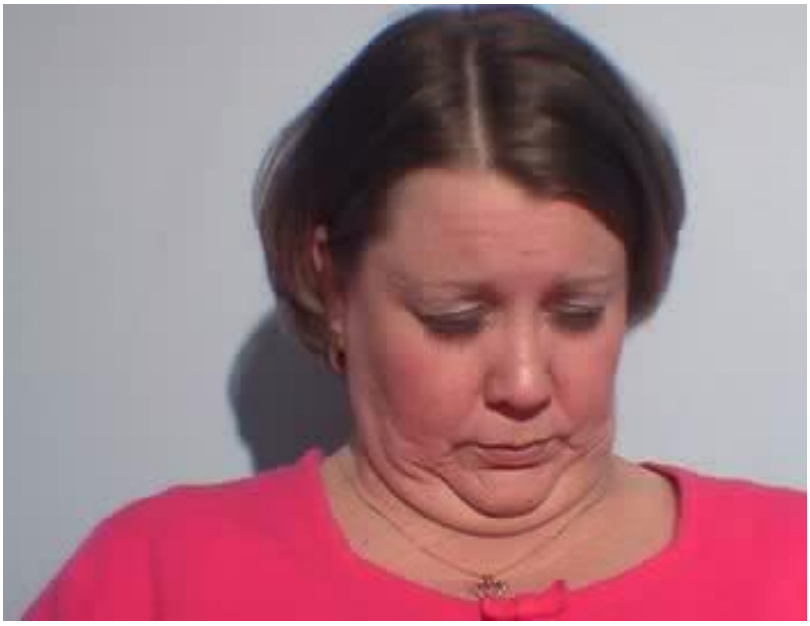
Norby et al. Parkinsonism Relat Disord 2015;21:1210-3





"Hyoid muscle" = submental muscle complex

Digastric, mylohyoid, suprahyoid, infrahyoid (sternohyoid and omohyoid)



Anterocollis

- **A form of cervical dystonia that may be more challenging to treat; patients with anterocollis (and retrocollis) are usually excluded from clinical trials of botulinum toxin, even though it is the treatment of choice**
- **Bilateral injection of sternocleidomastoid and scalene muscles may be associated with dysphagia and neck weakness**
- **Injection of submental complex is often effective, particularly when associated with jaw opening dystonia**
- **Longus colli may also contribute to anterocollis, but this muscle is difficult to approach, although it may be injected safely with imaging guidance** (Herting et al. Mov Disord 2004;19:588-90)

BoNT in Anterocollis Associated with Parkinson Disease

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To update the 2008 American Academy of Neurology (AAN) guidelines regarding botulinum neurotoxin for blepharospasm, cervical dystonia (CD), headache, and adult spasticity.

Methods: We searched the literature for relevant articles and classified them using 2004 AAN criteria.

Results and recommendations: Blepharospasm: OnabotulinumtoxinA (onaBoNT-A) and incobotulinumtoxinA (incoBoNT-A) are probably effective and should be considered (Level B). AbobotulinumtoxinA (aboBoNT-A) is possibly effective and may be considered (Level C). CD: AboBoNT-A and rimabotulinumtoxinB (rimaBoNT-B) are established as effective and should be offered (Level A), and onaBoNT-A and incoBoNT-A are probably effective and should be considered (Level B). Adult spasticity: AboBoNT-A, incoBoNT-A, and onaBoNT-A are established as effective and should be offered (Level A), and rimaBoNT-B is probably effective and should be considered (Level B), for upper limb spasticity. AboBoNT-A and onaBoNT-A are established as effective and should be offered (Level A) for lower-limb spasticity. Headache: OnaBoNT-A is established as effective and should be offered to increase headache-free days (Level A) and is probably effective and should be considered to improve health-related quality of life (Level B) in chronic migraine. OnaBoNT-A is established as ineffective and should not be offered for episodic migraine (Level A) and is probably ineffective for chronic tension-type headaches (Level B). *Neurology*® 2016;86:1818–1826

Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache

Report of the Guideline Development Subcommittee of the AAN

Simpson et al. Neurology 2016;86:1818-26

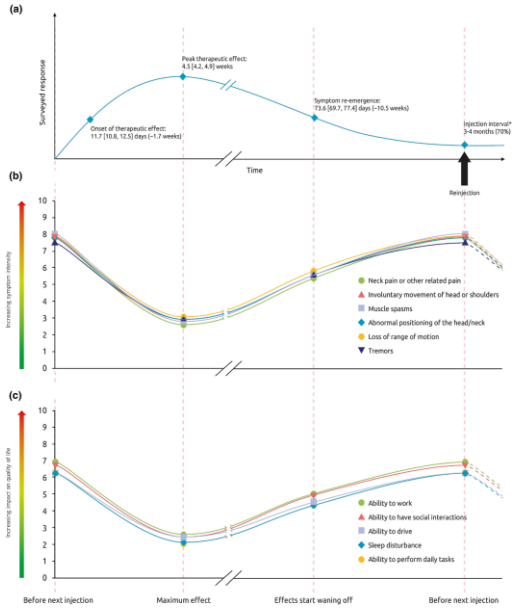
Indication	Level A Effective	Level B probably effective	Level C possibly effective	Level U insufficient evidence	Level A Ineffective	Level B ineffective
Blepharospasm		IncoA OnaA	AboA	RimaB		
Cervical dystonia	AboA RimaB	IncoA OnaA				
Upper-limb spasticity	AboA IncoA OnaA	RimaB				
Lower-limb spasticity	AboA OnaA			IncoA RimaB		
Chronic migraine	OnaA					
Episodic migraine					OnaA	
Tension-type headache						OnaA

Patient perspectives on the therapeutic profile of botulinum neurotoxin type A in cervical dystonia.

Comella et al. J Neurol 2020

- An internet-based survey was conducted through Carenity, a global online patient community, from May to September 2019.
- Eligible respondents were adults with CD who had ≥2 previous BoNT-A injections.
- Of 209 respondents (81% females; mean age of 49.7 years) 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.
- Treatment was not reported to completely abolish symptoms, even at peak effect.
- Symptom severity was strongest one day before the next session (~7–8/10).
- The impact of CD on quality of life followed the same ‘rollercoaster’ pattern.

Patient experiences of a BoNT-A response



Comella et al. J Neurol 2020

Patient perception of BoNT during Covid-19 pandemic

- **As the result of the shutdown, the inter-injection intervals increased from 11.2 ± 1.3 weeks to 17.7 ± 2.4 weeks delaying BoNT therapy by 6.6 ± 2.3 weeks.**
- **93% of the patients noticed increased muscle cramps and 82% increased muscle pain.**
- **Due to the shutdown, the patient's quality of life was reduced by 40.2 ± 19.5%; for patients with cervical dystonia this reduction was 41.1 ± 18.3%, for patients with blepharospasm 33.3 ± 15.3%, for patients with spasticity 37.8 ± 15.6%, for patients with pain condition 37.4 ± 35.7% and for patients with hemifacial spasm 27.5 ± 17.1%.**
- **After the shutdown 66% of patients perceived BoNT therapy as more important than before.**
- **91% of patients perceived long-term security of BoNT therapy availability as very important.**

Dressler D, Adib Saberi F. J Neural Transm 2020;127:1271-4

Movement Disorders
CLINICAL PRACTICE
2018;5: 273–82

RESEARCH ARTICLE

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

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Abstract

Background: Injectable daxibotulinumtoxinA (an investigational botulinum toxin, RT002) may offer a more prolonged duration of response—and therefore less frequent dosing—than onabotulinumtoxinA.

Objectives: To perform a phase 2, open-label, dose-escalation study to assess the efficacy and safety of daxibotulinumtoxinA in cervical dystonia.

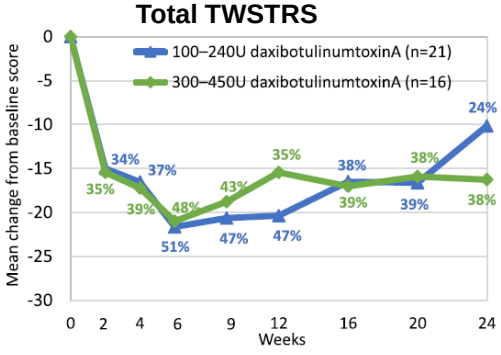
Methods: Subjects with moderate-to-severe isolated cervical dystonia were enrolled in sequential cohorts to receive a single open-label, intramuscular dose of injectable daxibotulinumtoxinA of up to 200 U (n = 12), 200–300 U (n = 12), or 300–450 U (n = 13; clinicaltrials.gov identifier NCT02706795).

Results: Overall, 33/37 enrollees completed the trial. DaxibotulinumtoxinA was associated with mean reductions in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score of 16.8 (38%) at week 4, 21.3 (50%) at week 6, and 12.8 (30%) at week 24. The proportion of subjects who were responders (achieved $\geq$ 20% reduction in TWSTRS-Total score) was 94% at week 6 and 68% at week 24. The median duration of response (time until $>$ 20% of the improvement in TWSTRS-Total score achieved at week 4 was no longer retained or re-treatment was needed) was 25.3 weeks (95% CI, 20.14–26.14 weeks). There were no serious adverse events and there was no apparent dose-related increase in the incidence of adverse events. The most common treatment-related adverse events were dysphagia (14%) and injection site erythema (8%).

Conclusions: Preliminary assessments suggest that injectable daxibotulinumtoxinA at doses up to 450 U is well tolerated and may offer prolonged efficacy in the treatment of cervical dystonia. Further studies involving larger numbers of patients are now warranted.

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 of effect**
- **Phase 3 study - ongoing**

Botulinum Toxin Treatment of Cervical Dystonia
Adverse events

- Usually mild and self-limiting and similar in both nature and severity between the different formulations
- Most common adverse events
  - Dysphagia
  - Neck muscle weakness
  - Injection site pain
  - 'Flu-like' symptoms
- Dose related and mostly owing to contiguous or distant spread of toxin
- Immunoresistance

toxins
2019;11(9)
Review

Immunogenicity Associated with Botulinum Toxin Treatment

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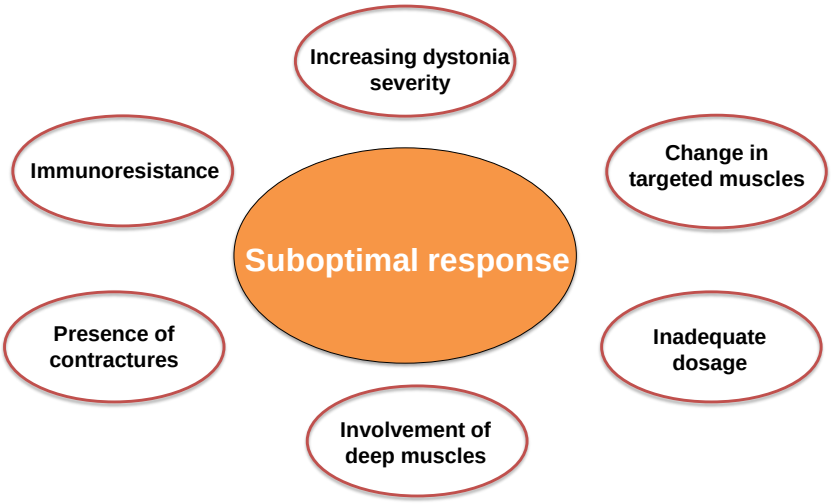
Received: 31 July 2019; Accepted: 22 August 2019; Published: 26 August 2019

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.

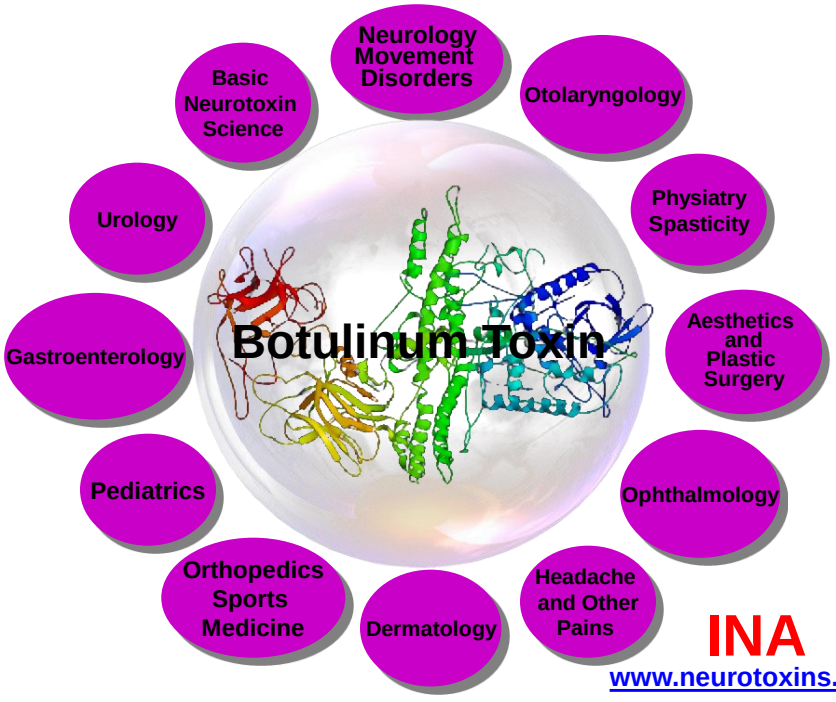
Considerations and strategies for suboptimal response or secondary non-response

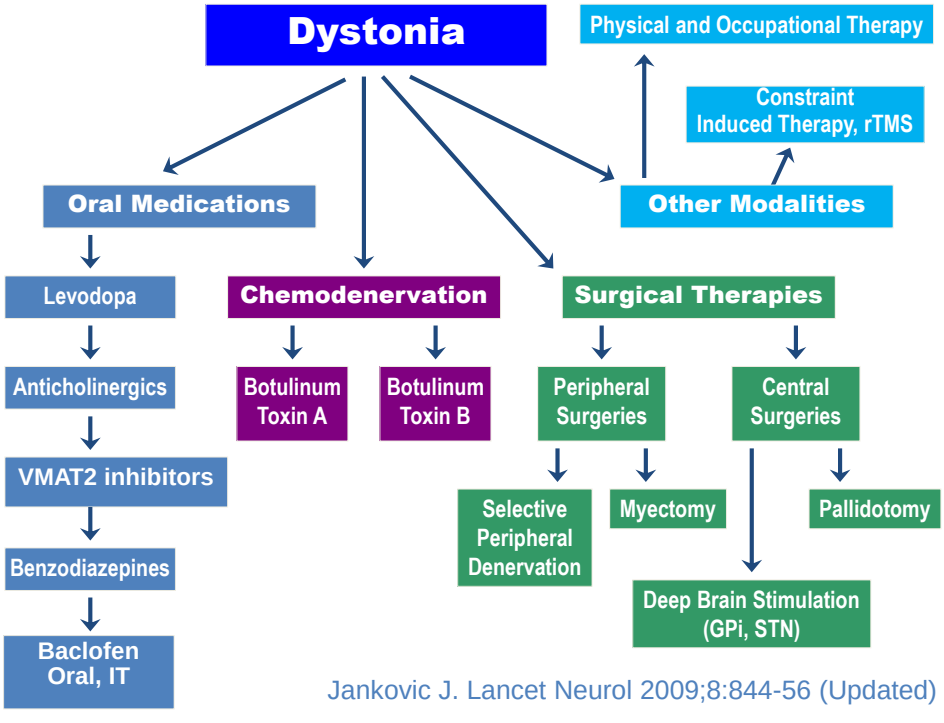


Thenganatt & Jankovic. In: Treatment of Dystonia, Dressler et al, eds, Cambridge University Press, Cambridge, UK; 2016

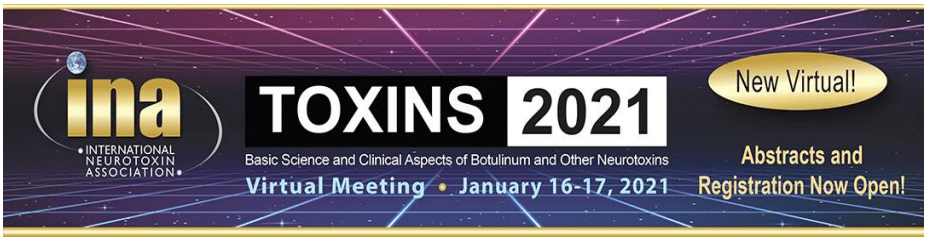
Botulinum Toxin - Summary

- **A potent biologic toxin – has emerged as one of the most versatile therapeutic agents in modern medicine**
- **When used by knowledgeable and skilled clinician it is one of the most reliably effective and safest drugs**
- **Establish realistic treatment goals**
- **Take a video (at least at baseline) and keep detailed records**
- **Patients must be educated about potential (transient) adverse effects and have realistic expectations about efficacy and duration of effect**
- **Be familiar with the regional anatomy**
- **Inject the agonist (not the antagonist, compensatory) muscle**
- **Be familiar with the properties and dosing of different products – dosages are not interchangeable**
- **Do not inject more often than every 3 months**
- **Designate specialized botulinum toxin clinics (single vial use)**
- **Try to optimize the benefits and reduce risk of adverse effects at each treatment visit – *don't give up***
- **Pre-certify all on-label and off-label uses**
- **Know the source (manufacturer, pharmacist, insurance company, patient)**





Jankovic J. Lancet Neurol 2009;8:844-56 (Updated)



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