Cervical Dystonia

9th Annual Cleveland Clinic Comprehensive Neurotoxin Course for Neurological Conditions

Joseph Jankovic, MD
Professor of Neurology, Distinguished Chair in Movement Disorders, Director, Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas

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
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.
Medical Treatment of Dystonia

Joseph Jankovic, MD*

Parkinson’s Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

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

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\textsubscript{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
• 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)

- Splenius capitis, 60-100 U
- Levator scapulae, 25-60 U
- Trapezius, 25-100 U
- Sternocleidomastoid, 40-70 U
- Scalene, 15-50 U

Some patients may require injections into additional muscles.
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**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>BoNT-A (OnaA; IncoA)</th>
<th>BoNT-A (AboA)</th>
<th>BoNT-B (RimaB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trapezius</td>
<td>35 – 100</td>
<td>100 – 250</td>
<td>1,500 – 5,000</td>
</tr>
<tr>
<td>Sternocleidomastoid</td>
<td>25 – 75</td>
<td>70 – 200</td>
<td>2,000 – 3,500</td>
</tr>
<tr>
<td>Splenius capitis</td>
<td>35 – 75</td>
<td>100 – 200</td>
<td>2,000 – 3,500</td>
</tr>
<tr>
<td>Levator scapulae</td>
<td>25 – 50</td>
<td>70 – 125</td>
<td>1,250 – 2,500</td>
</tr>
<tr>
<td>Scalene complex</td>
<td>25 – 60</td>
<td>70 – 150</td>
<td>1,250 – 3,000</td>
</tr>
</tbody>
</table>
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.

Diffusion, spread, and migration of botulinum toxin

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, suprathyroid, infrathyroid (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)
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 incBoNT-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 onaBoNT-A 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level A Effective</th>
<th>Level B probably effective</th>
<th>Level C possibly effective</th>
<th>Level U insufficient evidence</th>
<th>Level A Ineffective</th>
<th>Level B ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>IncoA</td>
<td>AboA</td>
<td>RimaB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>AboA RimaB</td>
<td>IncoA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper-limb spasticity</td>
<td>AboA IncoA OnaA</td>
<td>RimaB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower-limb spasticity</td>
<td>AboA OnaA</td>
<td></td>
<td>IncoA</td>
<td>RimaB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>OnaA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic migraine</td>
<td></td>
<td></td>
<td>OnaA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-type headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OnaA</td>
<td></td>
</tr>
</tbody>
</table>

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 $11.2 \pm 1.3$ weeks to $17.7 \pm 2.4$ weeks delaying BoNT therapy by $6.6 \pm 2.3$ 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 $40.2 \pm 19.5\%$; for patients with cervical dystonia this reduction was $41.1 \pm 18.3\%$, for patients with blepharospasm $33.3 \pm 15.3\%$, for patients with spasticity $37.8 \pm 15.6\%$, for patients with pain condition $37.4 \pm 35.7\%$ and for patients with hemifacial spasm $27.5 \pm 17.1\%$.
- 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
Injectable DaxibotulinumtoxinA in Cervical Dystonia: A Phase 2 Dose-Escalation Multicenter Study

Joseph Jankovic, MD,1,2 Daniel Tigges, MD,3 Atul T Patel, MD,4 Allison Brashear, MD,5 MBA,6 Marian Evatt, MD,7 Roman G Rubia, MD,8 Chad K. Oh, MD,7 Daniel Snyder, PhD,7 Gill Shears, PhD,7 and Cynthia Corrêa, MD9

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 300 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, 21.5% (50%) at week 6, and 30% at week 24. The proportion of subjects who were responders (achieved ≥ 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 maintained or re-treatment was needed) was 25.3 weeks (95% CI, 20.1–29.1 weeks).

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

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

- 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%
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
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)
Dystonia

- Oral Medications
  - Levodopa
  - Anticholinergics
  - VMAT2 inhibitors
  - Benzodiazepines
  - Baclofen (Oral, IT)
- Chemodenervation
  - Botulinum Toxin A
  - Botulinum Toxin B
- Surgical Therapies
  - Peripheral Surgeries
  - Central Surgeries
    - Selective Peripheral Denervation
    - Myectomy
    - Pallidotomy
    - Deep Brain Stimulation (GPI, STN)
- Other Modalities
  - Physical and Occupational Therapy
    - Constraint Induced Therapy, rTMS

Jankovic J. Lancet Neurol 2009;8:844-56 (Updated)
Parkinson’s Disease Center and Movement Disorders Clinic

www.jankovic.org

https://www.neurotoxins.org/toxins-2021/
https://www.neurotoxins.org/