Update on Treatment of Dystonia

David M. Swope MD
Professor of Neurology
Director, Division of Movement Disorders
UC Irvine

New 2013 Consensus Definition:

- Dystonia is a movement disorder characterized sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned, twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."
- Two Axis classification system (Axis I-- phenomenology and Axis II—possible causes)

- Albanese, Bhatia, Bressman, et al. "Phenomenology and Classification of Dystonia: a Consensus Update." Movement Disorders. 2013; 28: 863-873

Regions Affected

- **Focal.** Only one body region is affected. Typical examples of focal forms are blepharospasm, oro-mandibular dystonia, cervical dystonia, laryngeal dystonia, and writer's cramp. Cervical dystonia, is considered a form of focal dystonia, although by convention the shoulder can be included as well as the neck.
- **Segmental.** Two or more contiguous body regions are affected. Typical examples of segmental forms are: cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bi-brachial dystonia.
- **Multifocal.** Two non-contiguous or more (contiguous or not) body regions are involved.
- **Generalized.** The trunk and at least two other sites are involved. Generalized forms with leg involvement are distinguished from those without leg involvement.
- **Hemidystonia.** More body regions restricted to one body side are involved. Typical examples of hemidystonia are due to acquired brain lesions in the contralateral hemisphere.
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Commonly used oral medications for dystonia

Class of medication	Examples
Anticholinergics	benztropine, biperidin, ethopropazine, ophenadrine, procyclidine, trihexyphenidyl
Dopaminergics	levodopa, pramipexole, ropinirole, tetrabenazine
GABAergics	alprazolam, baclofen, chlordiazepoxide, clonazepam, diazepam
Muscle “relaxants”	baclofen, benzodiazepines, carisoprodol, chlorzoxazone, cyclobenzeprine, metaxolone, methocarbamol, orphenadrine
Others	carbamazepine, cannabidiol, cyproheptidine, gabapentin, lithium, mexilitine, nabilone, riluzole, tizanidine, zolpidem

Neurol Clin. 2015 Feb; 33(1): 77–100.

Botulinum toxin is first line treatment for focal dystonia

- Most effective in reducing pain and motor sx
- 80% of patients with CD and Bleph report good response
- Repeated tx—sustained symptomatic benefit, reduced latency effect, and prolonged duration of response
- Risk of developing neutralizing antibodies with current preparations—1.2%
- Side effects: CD—dysphagia; Bleph—ptosis, diplopia

Optimizing botulinum toxin therapy

- AAN practice guideline update published 2016
  - Blepharospasm:
    - onaBoNT-A, incoBoNT-A probably effective (level B)
    - aboBoNT-A possibly effective (level C)
  - Torticollis:
    - aboBoNT-A, rimaBoNT-A effective (level A)
    - onaBoNT-A, incoBoNT-A probably effective (level B)
- Botulinum toxin injection remains first line therapy for many, in particular focal dystonias such as cervical dystonia and blepharospasm
  - EMG-guidance has been found helpful in certain circumstances
  - growing interest in ultrasound guidance to improve outcomes by providing direct, non-invasive and real-time visualization of muscles to be injected

Comparison of the most common botulinum toxin formulations

	Onabotulinumtoxin A (Botox™)	**Abobotulinumtoxin A (Dysport™)**	**Incobotulinumtoxin A (Xeomin™)**	**Rimabotulinumtoxin B (Myobloc™)**
FDA-approved indications for dystonia	blepharospasm, cervical dystonia	cervical dystonia	blepharospasm, cervical dystonia	cervical dystonia
Preparation	vacuum dried	freeze dried	powder	liquid
Available dose sizes (units)	100, 200	300, 500	50, 100	1000, 2500, 5000
Storage	refrigerate	refrigerate	room temperature	refrigerate
Approximate dose equivalency*	1	2.5 – 3	1	40

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TMS treatment of Cervical Dystonia

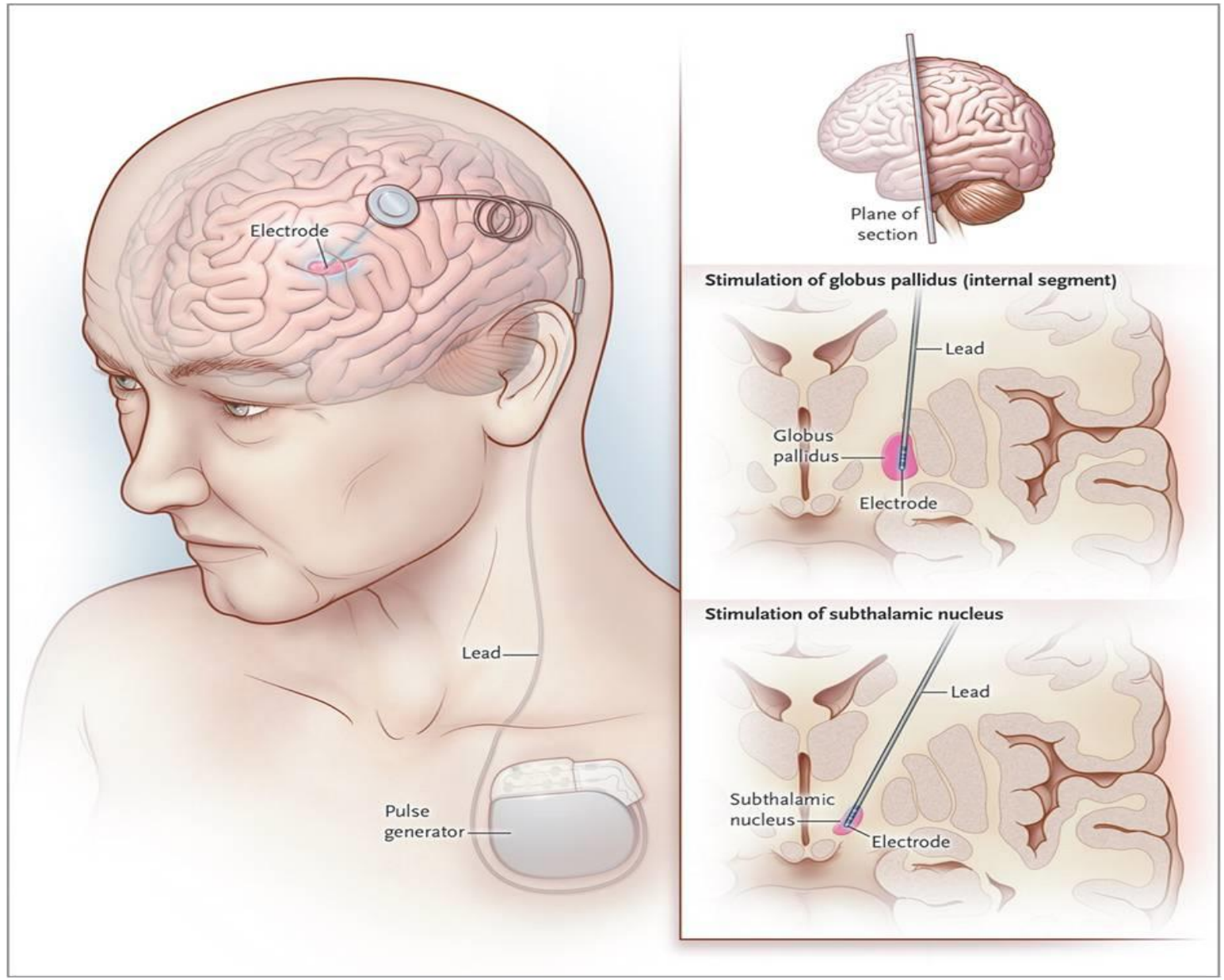
- 8 patients received 5 sessions of treatment with low frequency rTMS.
- Targets included primary motor cortex (MC), dorsal premotor cortex (dPM), supplementary motor area (SMA), anterior cingulate cortex (ACC), sham procedure.
- TWSTRS score improved with stimulation of dPM and MC between session 1 to session 5.

- Abnormal cerebellar connectivity and plasticity in isolated cervical dystonia
- PLoS One. 2015; 10(4): e0124937.
- Published online 2015 Apr 29. doi: 10.1371/journal.pone.0124937

DBS for Dystonia

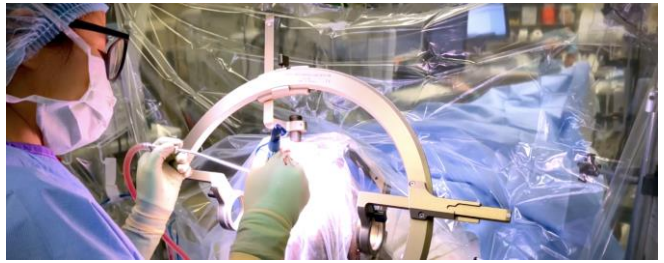
In general, the MAIN indications for surgery include:

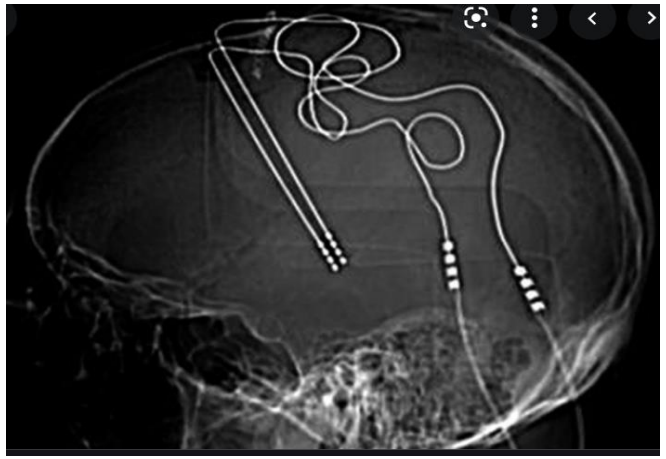
- Severe motor impairment
- Poor QOL,
- Severe pain
- Inability to perform ADL’s

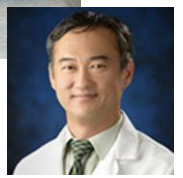

Electrode
Lead
Pulse generator
Plane of section
Stimulation of globus pallidus (internal segment)
Lead
Globus pallidus
Electrode
Stimulation of subthalamic nucleus
Lead
Subthalamic nucleus
Electrode

Augmenting the Good: Neuroplasticity and Surgical Treatment

- ✓ Deep Brain Stimulation
  - ✓ Implantation of electrodes to deep structures of the brain treats Parkinson's disease and many more disorders





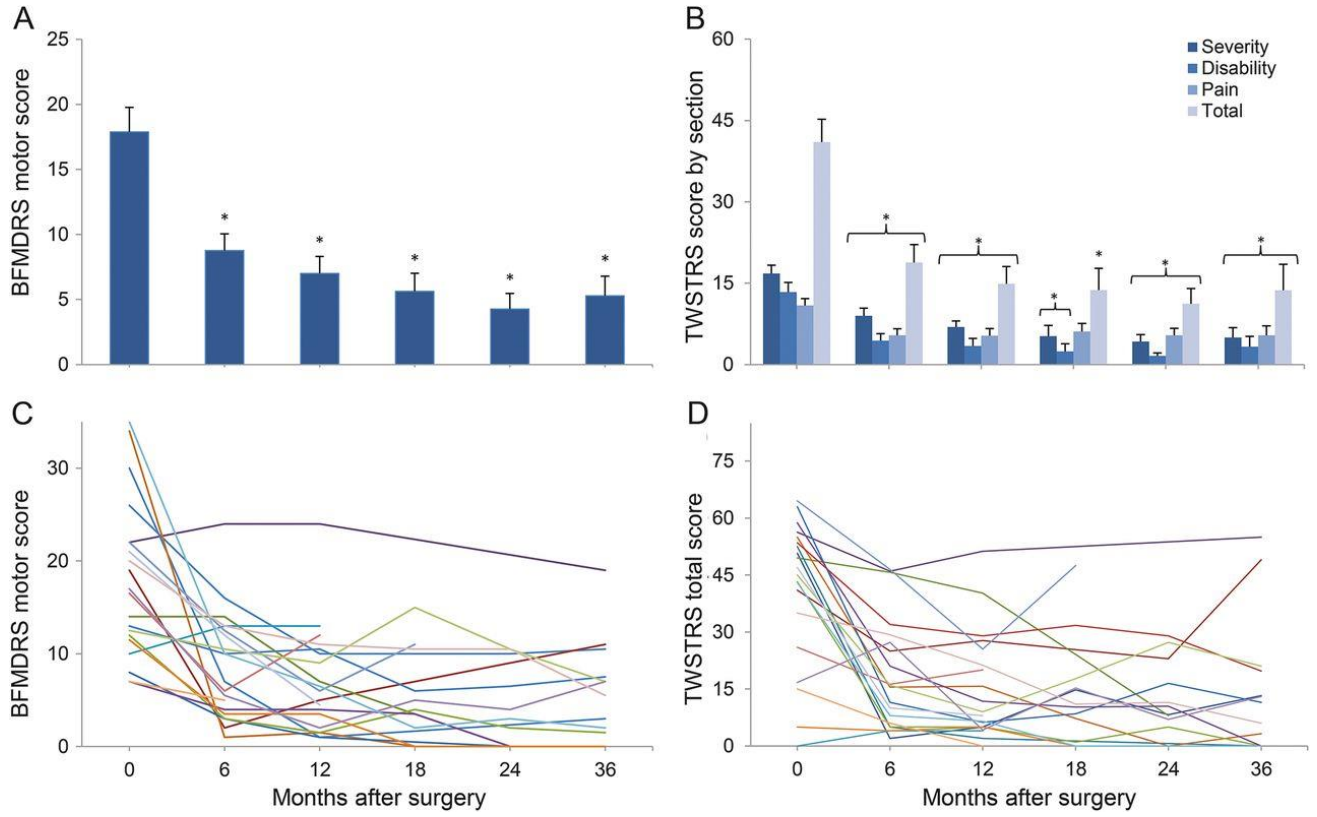


DBS for Dystonia

- Danish study, 12 patients with medically refractory dystonia (focal, multifocal, or generalized) received bilateral STN and GPi implants.
- Improvement on BFMDRS of 13.8 points with STN and 9.1 points with GPi stimulation.
- 4 patients rated on TWSTRS improved by 4.7% with GPi and 50.8% with STN stimulation.

- Lisbeth Schjerling M.D.[1,2], Lena E. Hjermind M.D., Ph.D.[3,4], Bo Jespersen M.D.[1], Flemming F. Madsen M.D., D.Sc.[1], Jannick Brennum M.D., D.Sc.[1], Steen R. Jensen R.N.[5], Annemette Løkkegaard M.D., Ph.D.[5] and Merete Karlsborg M.D.-Randomized Controlled Trial J Neurosurg. 2013 Dec;119(6):1537-45.
- doi: 10.3171/2013.8.JNS13844. Epub 2013 Oct 11.

DBS targeting STN in isolated dystonia
3 year follow up: significant and sustained improvement



Boston Scientific Website

Primary Author	Study Design	Sample Size	Follow Up	BFMDRS or TWSTERS	Change in Mean Scores BFMDRS or TWSTERS	% Improvement in BFMDRS and TWSTERS
Cersosimo et al, 2009[1]	Prospective Case Series	9	6 mos.	BFMDRS (Motor Scale)	• Baseline: 46.9 ± 24.3 • Post DBS: 24.1 ± 16.9	Not Reported
Houeto et al, 2007[2]	Prospective, Controlled, Multicenter	22	1 mo.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.1 • Post DBS*: 26.7 ± 14.9	Not Reported
Vidailhet et al, 2005[3]	Prospective, Controlled, Multicenter	22	12 mos.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.3 • Post DBS: 21 ± 14.1	51
Vidailhet at al, 2007[4]	Prospective, Controlled, Multicenter	22	36 mos.	BFMDRS (Motor Scale)	• Baseline: 46.3 ± 21.3 • Post DBS: 19.8 ± 17.4	58
Kiss et al, 2007[5]	Prospective, Single-Blind, Multicenter	10	12 mos.	TWSTERS (Severity Score)	• Baseline: 14.7 ± 4.2 • Post DBS: 8.4 ± 4.4	43
Kupsch et al, 2006[6]	Prospective, Controlled, Multi-center	40	6 mos.	BFMDRS (Motor Scale)	• Baseline: 36.4 ± 24.6 • Post DBS: 20.2 ± 18	46
Volkmann et al, 2012[7]	Prospective, Controlled, Multi-center	40	5 yrs.	BFMDRS (Motor Scale)	• Baseline: 43.4 ± 28.6 • Post DBS: 15.4 ± 16.3	60
Ostrem et al, 2011[8]	Prospective Pilot	9	12 mos.	TWSTERS (Total Score)	• Baseline: 53.1 ± 2.57 • Post DBS: 19.6 ± 5.48	62.9
Vidailhet et al, 2009[9]	Prospective	13	12 mos.	BFMDRS (Motor Scale)	• Baseline: 44.23 ± 21.12 • Post DBS: 34.69 ± 21.87	24.4

Long-term Outcomes of Pallidal Deep Brain Stimulation in X-linked Dystonia Parkinsonism (XDP): Up to 84 Months Follow-Up

- 11 patients implanted with bilateral GPi DBS between Oct. 2009 and Sept. 2018.
- BFMDRS mean score of 23.3 from mean baseline score of 36.3 one month after implant
- BFMDRS mean score or 13.7 at 12 months.
- 3 patients maintained benefit up to 72-84 months.

- Parkinsonism Relat Disord. 2019 Mar;60:81-86.doi: 10.1016/j.parkreldis.2018.09.022. Epub 2018 Sep 21. Joshua Emmanuel E Abejero [1], Roland Dominic G Jamora [2], Theodor S Vesagas [3], Rosalia A Teleg [4], Raymond L Rosales [5], Joseph P Anlacan [6], Monserrat S Velasquez [3], Jose A Aguilar

Summary

- Medical treatment of dystonia may be effective in some cases and can be used in conjunction with other treatments
- Botulinum toxin injections are treatment of choice for focal dystonia
- -very effective
- Transcranial magnetic stimulation still considered experimental
- Deep brain stimulation (DBS) can be effective in refractory cases

Parkinson's & Movement Disorders

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714-450-6701

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Anna E. Morenkova, MD, PhD

Nicolas M. Phielipp, MD

David Swope MD

UCI Health

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Laguna Hills, CA 92653
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UCI Health ALS & Neuromuscular Center
200 S. Manchester Avenue, Suite 110 Orange, CA 92868
ALS & Neuromuscular Disorders

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101 The City Drive South, Building 23 Orange, CA 92868
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UCI Medical Center
101 The City Drive South, Pavilion 1, Bldg. 30 Orange, CA 92868
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Tustin

UCI Health Tustin
1451 Irvine Blvd., Tustin, CA 92780
General Neurology, Movement

Yorba Linda

UCI Health Yorba Linda
18637 Yorba Linda Blvd.
Yorba Linda, CA 92886
General Neurology, Movement