Long-Term Efficacy, Safety, and Side Effect Profile of Botulinum Toxin Injections in Dystonia

A 20-year follow-up

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BACKGROUND

- Botulinum toxin (BoNT) injections have emerged as one of the most effective therapeutic modalities not only in neurology but in nearly all fields of medicine.
- The findings from the first double-blind, placebo-controlled trial of BoNT-A in cranial-cervical dystonia, conducted at Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) in 1987 (1), led to the approval of this treatment by the United States Food and Drug Administration (FDA) in 1989 (2).
- Since the initial approval, BoNT has been used to treat hundreds of different conditions (3-8).
- With the chronic use of BoNT and an expanding list of therapeutic indications there is a need to carefully examine the long-term efficacy and safety of BoNT treatment.
- Only a relatively small number of studies have followed patients receiving periodic injections over a period of at least 5 years or more (Table 1).

TABLE 1. ***Long-term studies of dystonia patients receiving BoNT injections including a follow-up period of at least 5 years***

Author	No. Pts.	% female	Mean age at 1st injection (yrs)	Mean follow-up (yrs)	Indication	BoNT type
Tan, et al., 1999 (9)	162	68.5%	57.9 ± 15.3	4.4 ± 3.8 (range: 0.3-10)	Oromandibular dystonia	OnabotulinumtoxinA
Kessler, et al., 1999 (10)	303	54.5%	41 (range: 17-69)	3.2 (range: 1.3- 5.9)	CD	AbobotulinumtoxinA
Hsiung, et al., 2002 (11)	235	60%	Range: 21-86	2-12	Various types of dystonia	OnabotulinumtoxinA
Haussermann, et al., 2004 (12)	100	57%	47.23 ± 14.28	5.0 ± 4.5	CD	AbobotulinumtoxinA
Skogseid, et al., 2005 (13)	78	65%	Range: 18-75	5.5 (range: 1.5-10)	CD	OnabotulinumtoxinA
Mejia, et al., 2005 (14)	45	71%	51.8± 11.6	15.8± 1.5	Various types of dystonia	BoNT-A and BoNT-B
Berman, et al., 2005 (15)	24	79%	60.4± 12.0 (range: 36-82)	2.1 ± 1.7 (range: 0.25-5.3)	CD	BoNT-B
Mohammadi, et al., 2009 (16)	207	60%	58± 27 (range: 22-95)	AbobotulinumtoxinA: 7.3± 31; OnabotulinumtoxinA: 5.0± 2.2	CD	OnabotulinumtoxinA and AbobotulinumtoxinA
Bentivoglio, et al., 2009 (17)	128	76.6%	57.7± 10.3 (range: 6- 81)	"15-year period"	Blepharospasm	OnabotulinumtoxinA and AbobotulinumtoxinA
Lungu, et al., 2011 (18)	20	25%	46.6± 9.45	13.6± 2.5	Focal hand dystonia	OnabotulinumtoxinA
Ramirez-Castaneda, et al., 2013 (19)	89	75.2%	49.7± 12.4 (range: 8.3-74.2)	18.5± 3.1 (range: 10-26.3)	Various types of dystonia	BoNT-A and BoNT-B

METHODS

- Subjects were identified from a search of our clinical database which includes every patient that has been injected with BoNT at any specific time in our center. This database provides information about age, sex, first initial visit, diagnosis code, and active status.
- Inclusion criteria:
  1. PDCMDC patients with a primary diagnosis of dystonia.
  2. BoNT treatment administered for at least 10 years.
  3. Patients who continued receiving treatment at least once a year.
- Out of a total of 1,636 patients treated with BoNT injection for any type of movement disorder during this period of time, 1361 had a therapeutic indication of dystonia. All subjects who met the inclusion-exclusion criteria were included in our analysis.
- Detailed demographic, clinical, treatment response, adverse events, and immunologic profile data is currently being entered from the 'Botulinum Toxin Data Form' into a database for analysis.

RESULTS

- Of 1,636 patients injected with BoNT at the PDCMDC, as early as September 1981, 1,361 patients had dystonia as a primary therapeutic indication of which 89 patients had continuous treatment of ≥ 1 injection visit per year for at least 10 years and continue receiving this treatment modality.
- The mean age at first injection was 49.7 ± 12.4 years (range: 8.3 to 74.2), and women were older (51.2 ± 10.0 years) than men (43.1 ± 15.9 years) (p = 0.003).

RESULTS (continued…)

TABLE 2. ***Demographics of long-term follow-up of 89 patients with dystonia treated periodically with BoNT injections***

Variable	Data
Total patients (n)	89
Age at first injection (yr)	49.72 ± 12.47
Age at last injection (yr)	68.29 ± 12.54
Interval follow-up period (yr)	18.56 ± 3.17
Gender, n (%), male/female	22 (24.71)/67 (75.28)
Number of visits	46.43 ± 13.29

Values: mean ± standard deviation

FIG. 1. ***Type of dystonia diagnoses in active patients treated with BoNT injections for the past two decades.*** **CD: cervical dystonia; Bleph: blepharospasm; OMD: oromandibular dystonia; SD: spasmodic dysphonia; focal dystonia includes: arm dystonia, writer's cramp dystonia, leg dystonia, and foot dystonia.**

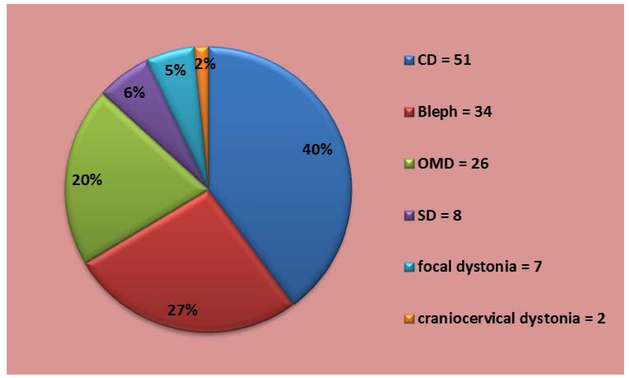
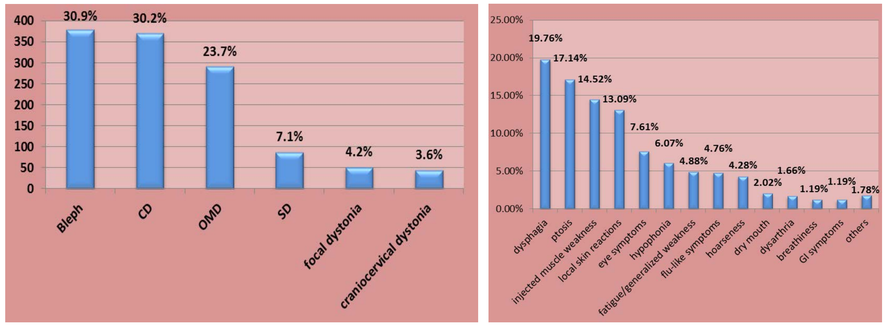


TABLE 3. ***Long-term follow-up of treatment efficacy of 89 patients receiving periodically BoNT injections for treatment of dystonia***

Parameter	Data
BoNT (units)	179.40 ± 135.35
BoNT type[1]: Botox®	95.25%
Efficacy (0-4 scale)	
Global rating effect	3.50 ± 0.84
Peak effect dystonia	3.72 ± 1.56
Latency of response (days)	3.74 ± 4.96
Duration of maximal response (weeks)	14.41 ± 6.22
Positive BoNT-A antibody test[2], n (%)	5/89 (5.61)
Adverse events, n (%)	840/4133 (20.32)

1. Myobloc 3.12%, other (study drugs) 1.06% and Dysport and Xeomin <1%.
2. 47 BoNT-A antibody tests were done in 35 patients, 6 were positive and 41 were negative.

FIG. 2. ***Adverse effects grouped per symptom and per diagnoses***



DISCUSSION

- In over three decades of experience with BoNT for the treatment of dystonia and other movement disorders at the PDCMDC, 89 patients received continuous BoNT treatment for two decades with persistent benefit and minimal adverse effects.
- Available data suggest that over time there is no significant change in latency and total duration of response to treatment (11, 14, 20-22).
- Long-term BoNT injections treatment has a favorable safety profile with mild and well-tolerated adverse events (23-24), good patient satisfaction (13), and low incidence of immunogenicity (10, 17, 25).
- Lack of response to BoNT treatment for dystonia and other movement disorders may occur for a myriad of reasons including inadequate dose, inappropriate muscle selection, concomitant drug therapy, dynamic disease change, and the development of neutralizing antibodies (14, 23, 26). In clinical practice poor or no response to BoNT is more frequently due to factors other than immunogenicity (10, 23-24).
- Our 20-year longitudinal study, coupled with published reports with at least 5-year follow-up (27), support the conclusion that BoNT is a safe and effective long-term treatment for focal and segmental dystonia.
- More prolonged clinical data are needed to describe the response and tolerability to this chronic treatment modality in dystonic conditions.

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