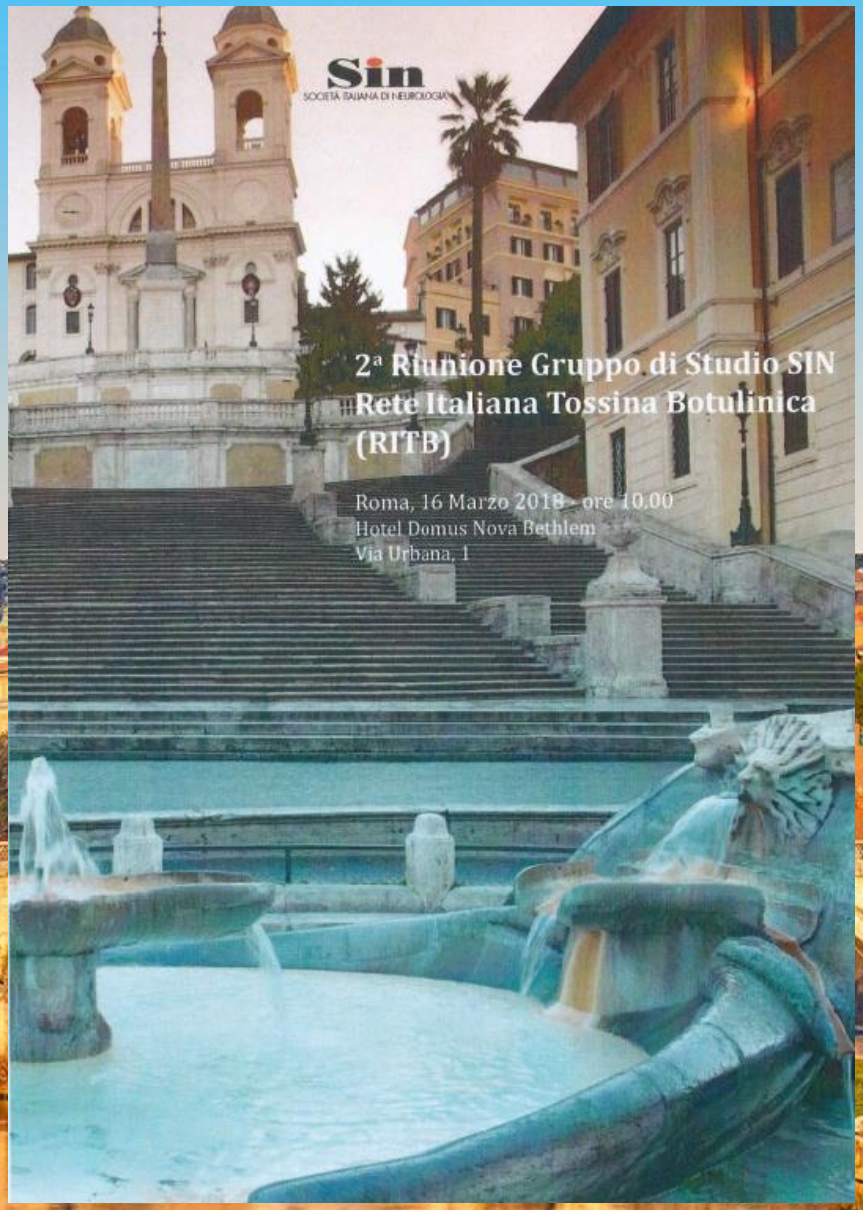


Prevenzione e trattamento degli effetti collaterali della terapia con neurotossina botulinica

Paolo Girlanda, *Messina*

The Food and Drug Administration defines an adverse event as any untoward medical occurrence that may be local or systemic

Terapia Botulinica

Eventi avversi

- **Effetti indesiderati prodotti dalla procedura**
- **Effetti indesiderati prodotti dal farmaco**

Effetti indesiderati prodotti dall'iniezione

Piccoli ematomi (palpebrali, etc…)
Ecchimosi
Dolore

J Neural Transm
DOI 10.1007/s00702-017-1809-5

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Botulinum toxin therapy in patients with oral anticoagulation: is it safe?

Christoph Schrader[1] · Markus Ebke[2] · Fereshte Adib Saberi[3] · Dirk Dressler[1]

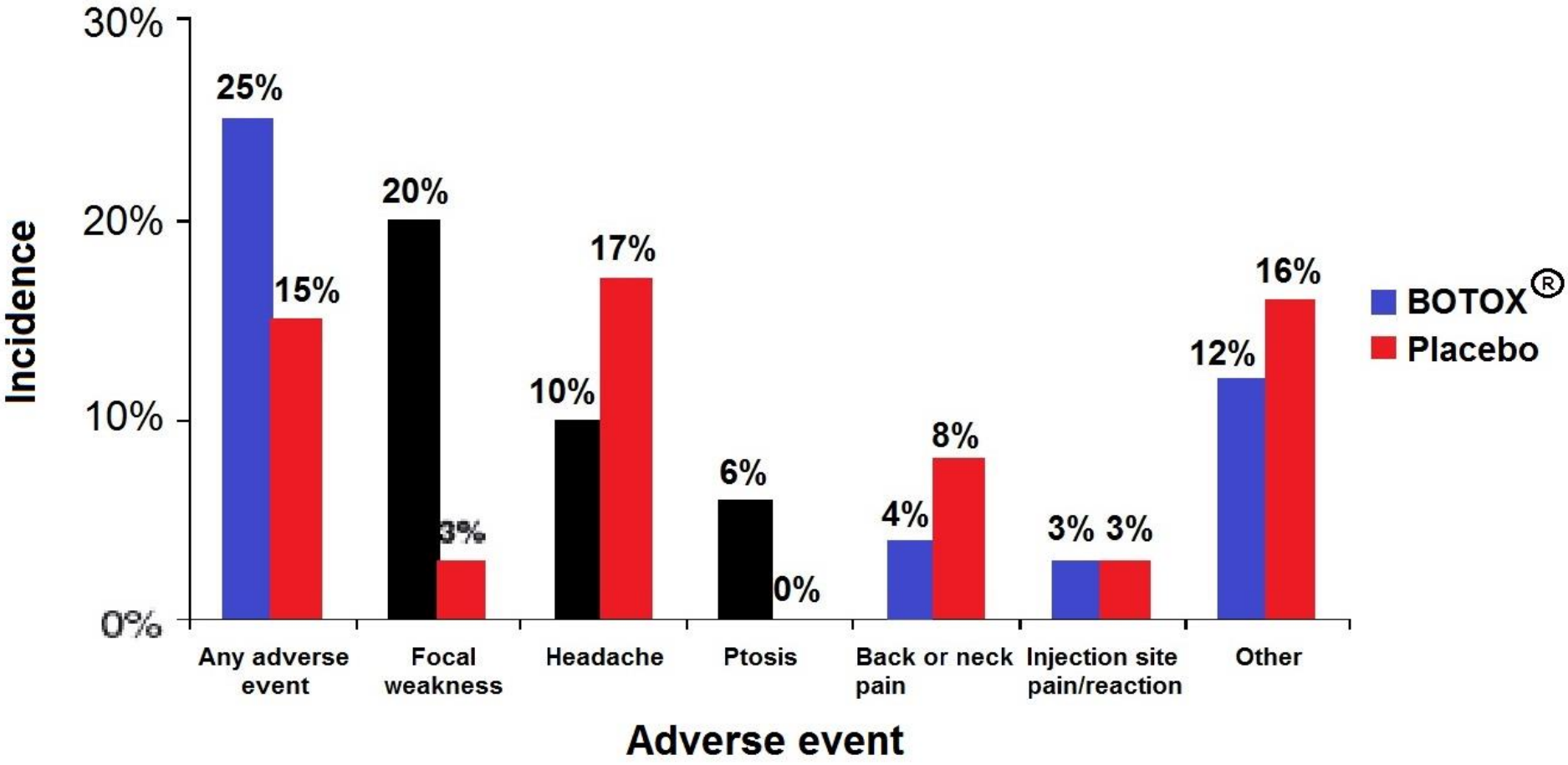
Interruption of oral anticoagulation to perform BT therapy is not justified.

Effetti indesiderati prodotti dal farmaco

- ✓ **Loco-regionali**
- ✓ **Generalizzati o Sistemici**
- ✓ **“A distanza”**

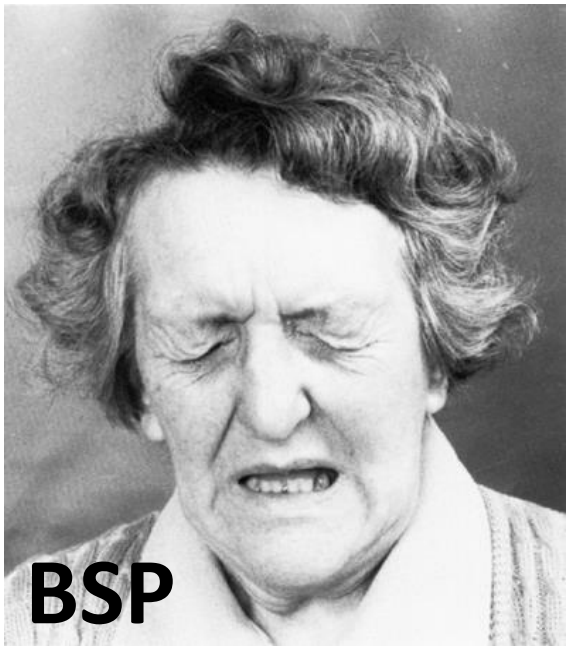
Meta-analysis assessing incidence of adverse events following BoNT-A and placebo treatment.

Naumann et al, European Journal of Neurology 2006



Effetti indesiderati loco-regionali: esempi

- ✓ **Ptosi**
- ✓ **Visione offuscata**
- ✓ **Diplopia**
- ✓ **Edema**
- ✓ **Secchezza della congiuntiva**
- ✓ **Lacrimazione eccessiva**



PREVENZIONE

- **Fattori di rischio**
- **Tecnica di infiltrazione**
- **Diluizione**
- **Dose**
- **Guida**

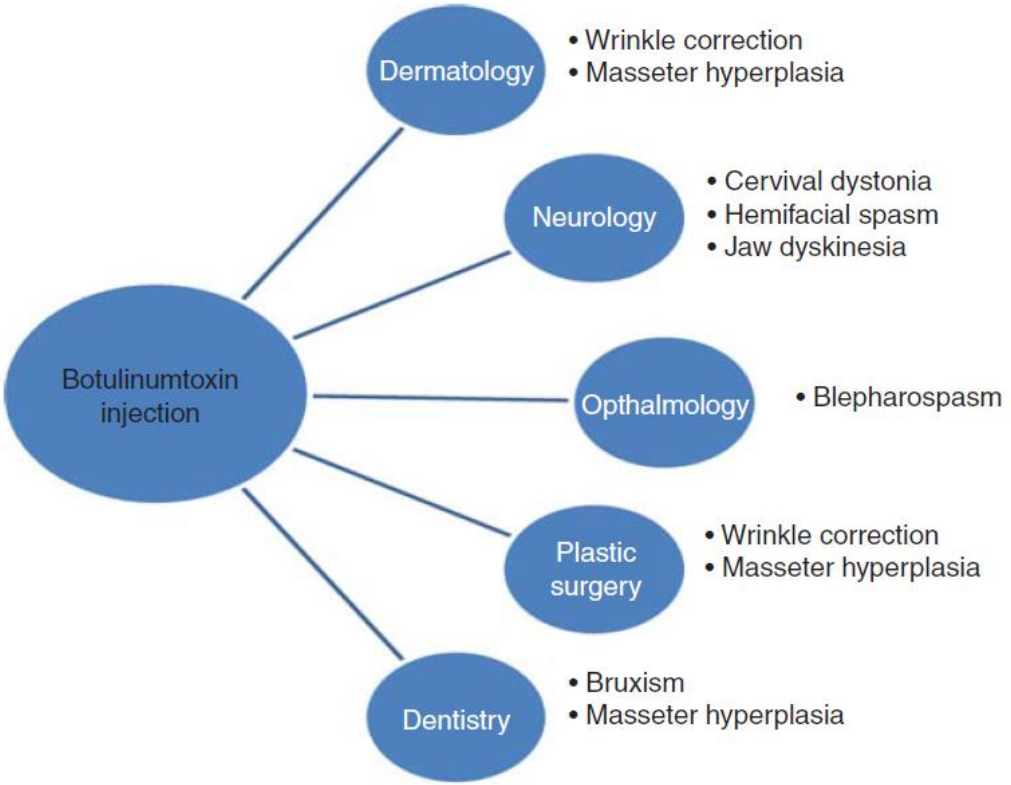
Journal of Dermatological Treatment, 2014; 25: 331–336

ISSN: 0954-6634 print / 1471-1753 online
DOI: 10.3109/09546634.2013.789473

ORIGINAL ARTICLE

Adverse events associated with botulinum toxin injection: A multidepartment, retrospective study of 5310 treatments administered to 1819 patients

Byung Wook Kim[1,*], Gyeong-Hun Park[1,*], Woo Jin Yun[1], Nark Kyoung Rho[3], Kyoung Ae Jang[3], Chong Hyun Won[1], Sung Eun Chang[1], Sun Ju Chung[2] & Mi Woo Lee[1]



184/5310 = 3.5%

Journal of Dermatological Treatment, 2014; 25: 331–336
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Muscle related	**113/184 = 61%**
Muscle unrelated	**71/185 = 39%**
Male	**37/184 = 20%**
Female	**147/184 = 80%**

Journal of Dermatological Treatment, 2014; 25: 331–336

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informa
healthcare

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Muscle-related adverse events	*n*	Secretion, injection-related adverse events, etc.	*n*
Double vision	4	Arm pain	1
Drooling	10	Bruise	8
Dysphagia	6	Congestion	1
Eyebrow elevation	5	Dry mouth	5
Eyelid motion abnormality	6	Dissatisfaction	22
Head drop	2	Dizziness	1
Hemifacial weakness	17	Eyelid edema	2
Mastication discomfort	3	Edema	16
Mouth asymmetry	4	Erythema	1
Nasal wrinkle formation	5	Eye pain	5
Neck discomfort	7	Headache	4
Neck pain	1	Lower lid bulging	3
Ptosis	42	Secretion increase	1
Retrocollis	3	Pain	1

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Target disease	Total treatment	All treatments with adverse events	Treatments with muscle-related adverse events	Treatments with muscle-unrelated adverse events
Upper face wrinkles	520	20	10	10
Blepharospasm	693	52	34	19
Cervical dystonia	1527	26	20	6
Hemifacial spasm	2258	84	50	34
Jaw dyskinesia	103	1	0	1
Masseter hyperplasia	209	1	0	1

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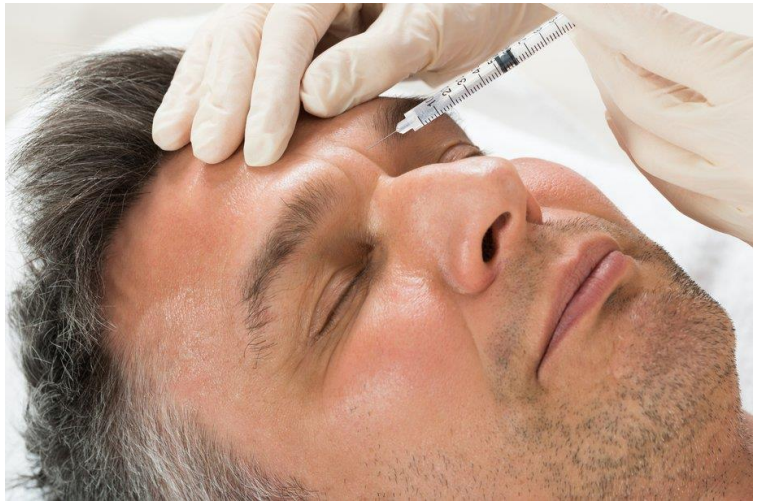
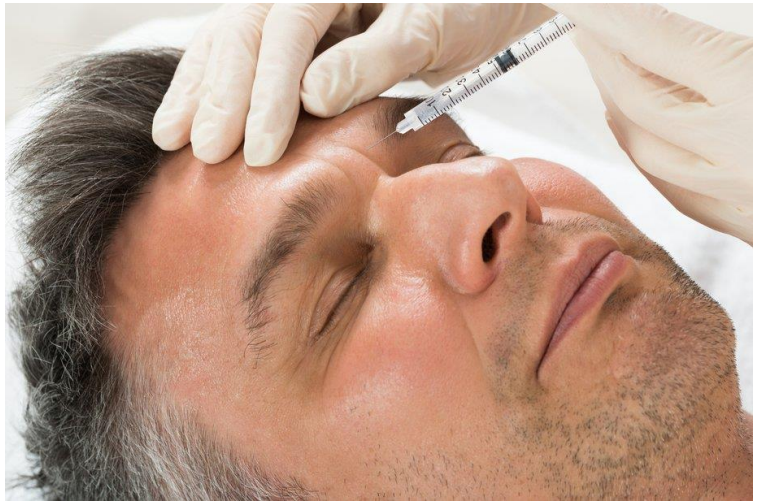
Target disease	All treatments with adverse events (%)	Treatments with muscle-related adverse events (%)	Treatments with muscle-unrelated adverse events (%)
	Incidence	Incidence	Incidence
Male	2.82	1.61	1.29
Female	4.05	2.49	1.53
OnabotulinumtoxinA (Botox)	3.44	1.92	1.52
AbobotulinumtoxinA (Dysport)	5.22	3.99	1.15
Upper face wrinkles	3.94	1.96	1.96
Blepharospasm	8.29	5.27	3.06
Cervical dystonia	1.76	1.32	0.44
Hemifacial spasm	4.17	2.43	1.67
Jaw dyskinesia	1.07	0.00	1.07
Masseter hyperplasia	0.49	0.00	0.49

- Fattori di rischio
- Tecnica di infiltrazione
- Diluizione
- Dose
- Guida



- Fattori di rischio
- Tecnica di infiltrazione
- Diluizione
- Dose
- Guida



Effect of Volume and Concentration on the Diffusion of Botulinum Exotoxin A

Arch Dermatol. 2004;140:1351-1354

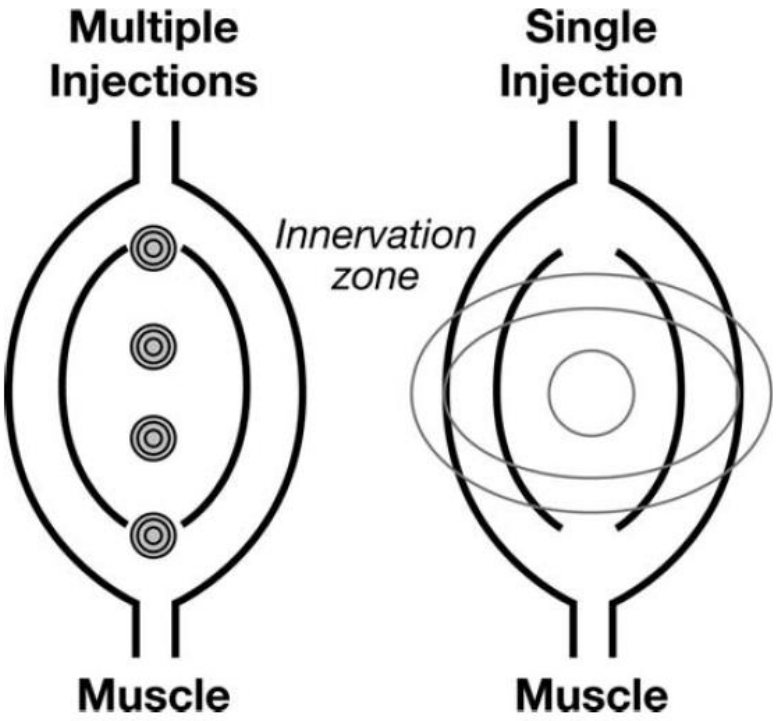
T. S. Jeffrey Hsu, MD; Jeffrey S. Dover, MD, FRCPC; Kenneth A. Arndt, MD

REVIEW

Diffusion, Spread, and Migration of Botulinum Toxin

Juan Ramirez-Castaneda, MD,[1] Joseph Jankovic, MD,[1*] Cynthia Comella, MD,[2] Khashayar Dashtipour, MD, PhD,[3] Hubert H. Fernandez, MD,[4] and Zoltan Mari, MD[5]

Movement Disorders, Vol. 28, No. 13, 2013



EXPERT REVIEWS

Ultrasound-guided botulinum toxin injections in neurology: technique, indications and future perspectives

Expert Rev. Neurother. 14(8), 923–936 (2014)

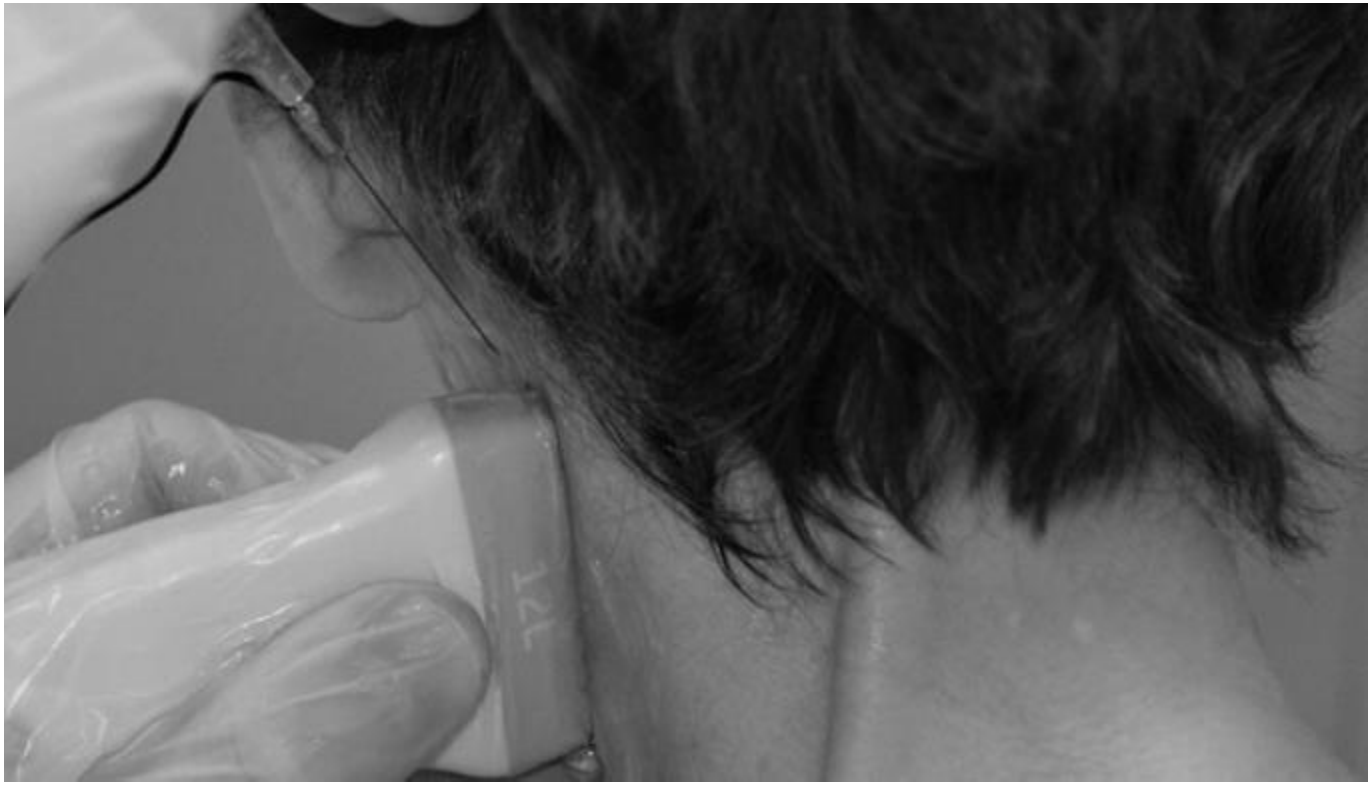
Uwe Walter*[1] and Dirk Dressler[2]

Small randomized studies suggest that US-guidance can improve therapeutic efficacy and reduce adverse effects of BT therapy when compared to conventional placement.

ELIMINATION OF DYSPHAGIA USING ULTRASOUND GUIDANCE FOR BOTULINUM TOXIN INJECTIONS IN CERVICAL DYSTONIA

JUSTIN S. HONG, MD, GEETA G. SATHE, MD, CHRISTIAN NIYONKURU, MS, and MICHAEL C. MUNIN, MD

Muscle Nerve **46:** 535–539, 2012



Neurotox Res (2012) 22:265–273
DOI 10.1007/s12640-012-9314-y

REVIEW

Efficacy and Safety of Long-term Botulinum Toxin Treatment in Craniocervical Dystonia: A Systematic Review

Carlo Colosimo · Dorina Tiple · Alfredo Berardelli

This article reviews the data from clinical trials that have assessed the long-term results of botulinum neurotoxin type A (BoNT-A) and type B in the treatment of the different forms of focal craniocervical dystonia, cervical dystonia (CD), blepharospasm, oromandibular, and laryngeal dystonia.

The incidence of adverse effects usually declines after the first treatment session, probably owing to a learning curve of the treating physician

Botulinum Toxin A Treatment for Primary Hemifacial Spasm

Arch Neurol. 2002;59:418-420

A 10-Year Multicenter Study

Giovanni Defazio, MD; Giovanni Abbruzzese, MD; Paolo Girlanda, MD; Laura Vacca, MD; Antonio Currà, MD; Roberto De Salvia, MD; Roberta Marchese, MD; Roberto Raineri, MD; Francesco Roselli, MD; Paolo Livrea, MD; Alfredo Berardelli, MD

Table 2. Comparison of Adverse Events at the Beginning of 10 Years of Botulinum Toxin A Treatment in 65 Patients With Primary Hemifacial Spasm

Adverse Events	1st Year	10th Year	*P* Value*
Upper lid ptosis			
Patients, No. (%)	15 (23)	5 (8)	.03
Treatment sessions, No. (%)	21/239 (9)	5/232 (2)	.003
Duration, mean ± SD, wk	3.0 ± 2.0	2.6 ± 0.5	.07
Facial weakness on the side of injection			
Patients, No. (%)	7 (11)	3 (5)	.30
Treatment sessions, No. (%)	10/239 (4)	3/232 (1)	.10
Duration, mean ± SD, wk	3.5 ± 1.1	3.2 ± 0.5	.66
Diplopia			
Patients, No. (%)	2 (3)	0	.47
Treatment sessions, No. (%)	3/239 (1)	. . .	.28
Duration, mean ± SD, wk	4 ± 0	. . .	NS†

Effetti indesiderati sistemici:

- Malessere generale
- Rash cutaneo
- S. simil-influenzale
- Nausea

Clin Neuropharmacol. 2010 ; 33(5): 243–247.

Systemic Weakness After Therapeutic Injections of Botulinum Toxin A: A Case Series and Review of the Literature

Beth E. Crowner, Diego Torres-Russotto, Alexandre R. Carter, and Brad A. Racette

Literature Review. 16 cases – Age: 15 m – 67 y – [Spast., CD, CP, HD]
Dose: Dysport: [250-1000] - Botox: [100-800]
Duration: 4w – 3m

Risk of developing systemic effects does not appear to be related to dose based on body weight.

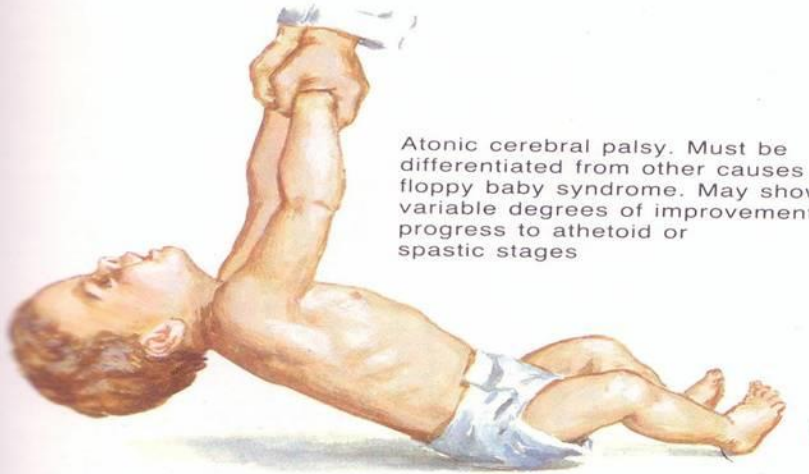
It may be more likely that risk for systemic effects is related to total injection dose and injection frequency.

We would recommend careful consideration of re-injection frequency if injections of greater than 600 units of Botox are given.

JAMA, June 10, 2009—Vol 301, No. 22

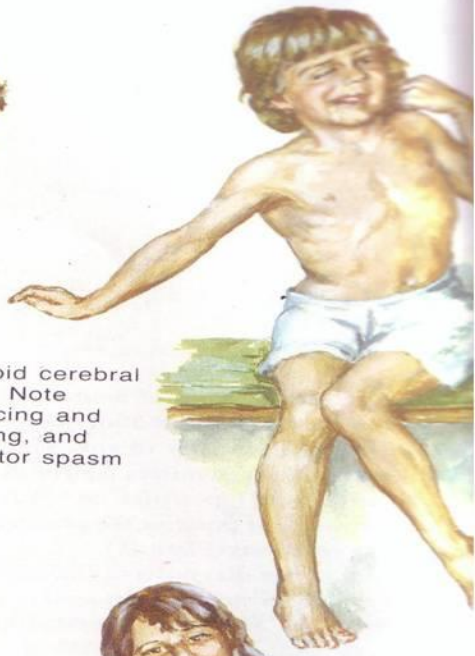
FDA Requires Black Box Warnings on Labeling for Botulinum Toxin Products

Cerebral Palsy



Atonic cerebral palsy. Must be differentiated from other causes of floppy baby syndrome. May show variable degrees of improvement or progress to athetoid or spastic stages

Athetoses and persistent asymmetric tonic neck reflex

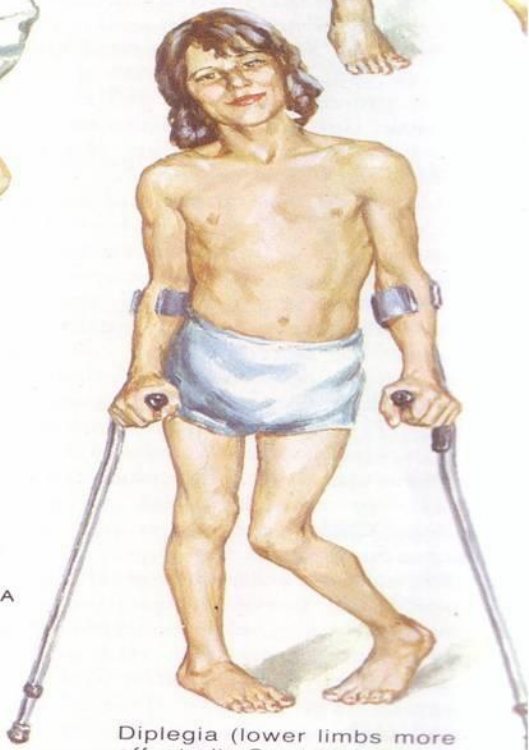


Athetoid cerebral palsy. Note grimacing and drooling, and adductor spasm

Ataxic cerebral palsy. Wide gait, tendency to fall, inability to walk straight line

Hemiplegia on right side. Hip and knee contractures and talipes equinus. Astereognosis may be present

Spastic quadriplegia. Characteristic "scissors" position of lower limbs due to adductor spasm



Diplegia (lower limbs more affected). Contractures of hips and knees and talipes equinovarus (clubfoot)

Toxins **2015**, *7*, 4645-4654; doi:10.3390/toxins7114645

OPEN ACCESS

toxins

ISSN 2072-6651

www.mdpi.com/journal/toxins

Article

Questionnaire about the Adverse Events and Side Effects Following Botulinum Toxin A Treatment in Patients with Cerebral Palsy

Izabela Blaszczyk [†,*], Nazli Poorsafar Foumani [†], Christina Ljungberg and Mikael Wiberg

SYMPTOMS	NO	YES	IF "YES" PLEASE COMMENT AND SPECIFY
GENERAL WEAKNESS			
FATIGUE			
FLU LIKE SYMPTOMS			
PNEUMONIA			
BREATHING DIFFICULTIES			
SWALLOWING DIFFICULTIES			
SPEECH DIFFICULTIES			
DRY MOUTH			
DIARRHOEA			
URINARY INCONTINENCE			
LOCALIZED MUSCLE WEAKNESS			
PAIN			
ITCH			
RASH			
HEMATOMA AT INJECTION SITE			
OTHER SYMPTOMS			

Table 1. Characteristics of participants.

n	Sex (M:F)	Age (y:mo)	Weight (kg)	CP Type	GMFCS
74	41:33	13:6 (SD 7:8)	37 (SD 20)	USCP 18 BSCP 38 DYSK 16 MIX 2	I–III 28 IV–V 46

M: male; F: female; y: year; mo: months; CP: cerebral palsy; USCP: unilateral spastic cerebral palsy; BSCP: bilateral spastic cerebral palsy; DYSK CP: dyskinetic cerebral palsy; MIX CP: mixed type of cerebral palsy; GMFCS: Gross Motor Function Classification System.

Table 2. Incidence of adverse events (number of treatments = 105, number of patients = 74, F/M = 33:41).

Adverse Event's Type (*n*)	*n* (%) AEs	*n* (%) Treatments	*n* (%) Patients	*n* (%) Female	*n* (%) Male
All Adverse Events	95 (100)	54 (51)	45 (61)	21 (64)	24 (59)
Generalized (systemic) adverse events (26) generalized muscle weakness (18), fatigue (3), flu-like symptoms (5)	50 (53)	33 (31)	28 (38)	17 (51)	11 (27)
Focal distant adverse events (24) swallowing difficulties (5),speech disorders (3), dry mouth (4), drooling (2), respiratory troubles (2), pneumonia (1), diarrhoea (1), nosebleeds (2), hot flashes (1), urinary incontinence (3)					
Focal local adverse events (22) local muscle weakness (15), pain at the site of injection (3), itching (1), rush (1), swelling at injection site (1), cold hands (1)	45 (47)	30 (29)	27 (37)	12 (36)	15 (37)
Procedural adverse events (23) bruising (19), leakage (2), no effect of treatment (2)					

AEs: adverse events.

Table 3. Risk for generalized and focal distant adverse events after BoNT-A treatment.

Variable	Odds Ratio	*p*-Value	95% CI	Relative Risk	95% CI
Gender: F/M	2.564	0.029	1.101–5.973	1.899	1.060–3.400
Total dose (U): ≥400/<400	2.171	0.095	0.875–5.390	1.651	0.945–2.885
Body weight (kg): ≥45/<45	1.662	0.285	0.654–4.223	1.432	0.725–2.831
Number of treated body parts (*n*): ≥6/<6	1.214	0.667	0.501–2.940	1.141	0.631–2.063
GMFCS level: IV–V/I–III	1.080	0.866	0.442–2.636	1.054	0.568–1.955
Age (y): ≥10/<10	0.975	0.952	0.424–2.242	0.982	0.554–1.741
Dose (U/kg): ≥10/<10	0.809	0.618	0.352–1.859	0.866	0.492–1.523

F: female; M: male; CI: confidence interval; GMFCS: Gross Motor Function Classification System.

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY

PUBLICATION DATA
Accepted for publication 15th December 2017.
Published online

ORIGINAL ARTICLE

Severity of cerebral palsy and likelihood of adverse events after botulinum toxin A injections

CAITLYN M SWINNEY[1] | KAREN BAU[2] | KAREN L OAKLEY BURTON[2] | STEPHEN J O'FLAHERTY[3] | NATASHA L BEAR[4] | SIMON P PAGET[2]

Injecting episodes n=2219

Episodes with follow-up n=2158 (97.3%)

- Adverse events reported at the time of botulinum toxin A injection occurred in 6% of injection episodes.
- Adverse events were reported at follow-up in 22% of injection episodes.
- Children in Gross Motor Function Classification System (GMFCS) levels IV and V have increased rates of systemic adverse events.

Gross Motor Function Classification System (GMFCS)

AE at follow-up
- Systemic 9 %
- Local weakness 11 %

European Journal of Neurology 2010, **17** (Suppl. 2): 9–37

Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement

S. C. Love[a], I. Novak[b], M. Kentish[c], K. Desloovere[d], F. Heinen[e], G. Molenaers[f], S. O'Flaherty[g] and H. K. Graham[h]

- **Conversion factors between different preparations of BoNT-A can lead to life threatening miscalculations and their use is strongly discouraged. Rates and sizes of reactions may be different between preparations (level A).**
- **Determination of dose relates to severity of spasticity, goal of treatment, size of targeted muscle, distribution of neuromuscular junctions with that muscle and previous responses to BoNT-A (if known).**
- **Dose should be cautiously selected in patients of GMFCS level V and any patient with dysphagia or breathing problems.**
- **Precise localization of muscle injection sites helps to improve the safety profile of BoNT-A by reducing the likelihood of unwanted toxin migration (level U)*. Use injection techniques which allow the operator to accurately isolate the target muscle (ultrasound is the preferred method).**

European Journal of Neurology 2010, **17** (Suppl. 2): 9–37

Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement

S. C. Love[a], I. Novak[b], M. Kentish[c], K. Desloovere[d], F. Heinen[e], G. Molenaers[f], S. O'Flaherty[g] and H. K. Graham[h]

Table 3 Products and doses

	Dose U/kg body weight		
Product	Range in literature	Recommendation	Maximum Total Dose
BOTOX®	6–24 U/Kg (up to 30 U/Kg used in occasional multilevel injections)	GMFCS I–IV without risk factors: 16–20 U/Kg GMFCS V with risk factors: 12–16 U/Kg*	< 300 U [53,57] < 400–600 U [79]
Dysport®	10–30 U/Kg	20 U/Kg [52] (level B recommendation)	200–500 U [54] (level U Recommendation) < 900 U [79]

Risk factors include symptoms and signs of pseudobulbar palsy, swallowing difficulties, history of aspiration and respiratory disease. When risk factors are present, evaluate the level of risk and either further reduce the total dose or avoid using BoNT-A.
*Expert opinion.

"U" stands for "insufficient data to support or refute use of a particular treatment or diagnostic test," not unimportant or useless. The article emphasizes, "...a Level U guideline recommendation is not synonymous with a negative recommendation."

Effetti indesiderati sistemici:

Produzione di anticorpi e mancata risposta alla terapia

Naumann et al Neural Transm (2013):

- **The immunogenicity rate for all type A botulinum neurotoxins is low**
- **The type B serotype formulation appears to be more immunogenic**
- **Treatment failure and secondary non-response to botulinum neurotoxin products are often the result of factors other than the presence of neutralizing antibodies.**

Naumann et al Neural Transm (2013):

- Clinical strategies to reduce or eliminate potential risk factors that may lead to the development of neutralizing antibodies are to be considered.
- At the present time an accepted strategy is to mitigate antibody formation using the lowest effective doses that produce a meaningful therapeutic effect and employing the longest inter-injection interval that is clinically acceptable.

J.J. Chen, and K. Dashtipour PHARMACOTHERAPY, 2013

- Studies indicate that neutralizing antibodies develop in up to 2% of BoNT-A treated patients. However, higher rates have been reported (pediatric patients , patients with hyperactive detrusor muscles).
- Among the BoNT-A products, comparative differences in the risk of immunogenicity remains surrounded by unresolved issues.
- If immunoresistance develops to one BoNT serotype, another serotype may be used successfully.

J.J. Chen, and K. Dashtipour PHARMACOTHERAPY, 2013

- Greater risk for the formation of BoNT NAB: short dosing intervals, use of booster doses, greater total cumulative dose, greater number of treatment cycles, longer duration of treatment, and greater number of injection sites.
- Other causes of nonresponse: improper target site injection, mishandling of the BoNT product (e.g., improper reconstitution, dilution, storage), use of insufficient dosage and the patient's self-reported perception of clinical effect.

Toxicon 107 (2015) 72–76

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Review

Is it time for flexibility in botulinum inter-injection intervals?

Oluwadamilola O. Ojo [a, b, 1], Hubert H. Fernandez [a, c, *]

La tossina botulinica può essere considerata un farmaco con un buon profilo di sicurezza

… in mani esperte

Grazie per la vostra attenzione