USE OF BONT IN NONDYSTONIC DISORDERS

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DISCLOSURE

- Dr Truong received research funding in 2015 from Dysport, Merz, Abvie. Adamas

CLINICAL DEVELOPMENT OF BOTULINUM TOXIN

- The clinical development of botulinum toxin began in the late 1960's with the search for an alternative to surgical re-alignment of strabismus BY Allen Scott.
- Daniel Drachman, a renowned neuroscientist at Johns Hopkins University, and his work, in which he had been injecting minute amounts of botulinum toxin directly into the hind limb of chickens to achieve local denervation (Drachman, 1964).
- Drachman introduced Scott to Edward Schantz (1908-2005) who was producing purified botulinum toxins for experimental use and generously making them available to the academic community.
- Schantz himself credits Vernon Brooks with the idea that botulinum toxin might be used for weakening muscle (Schantz, 1994).

BOTULINUM TOXIN IN DYSTONIA

- Stanley Fahn's group at Columbia University in 1985reported the first double-blind study testing the use of Scott's toxin in blepharospasm (Fahn, 1985).
- Also in 1985, Tsui and colleagues reported the successful use of botulinum toxin for the treatment of cervical dystonia in 12 patients (Tsui et al, 1985).
- This was followed by the first double-blind, crossover study in which botulinum toxin was found to be significantly superior to placebo at reducing the symptoms of cervical dystonia, including pain (Tsui et al, 1986).

CLINICAL APPLICATIONS CONTINUED TO EXPAND

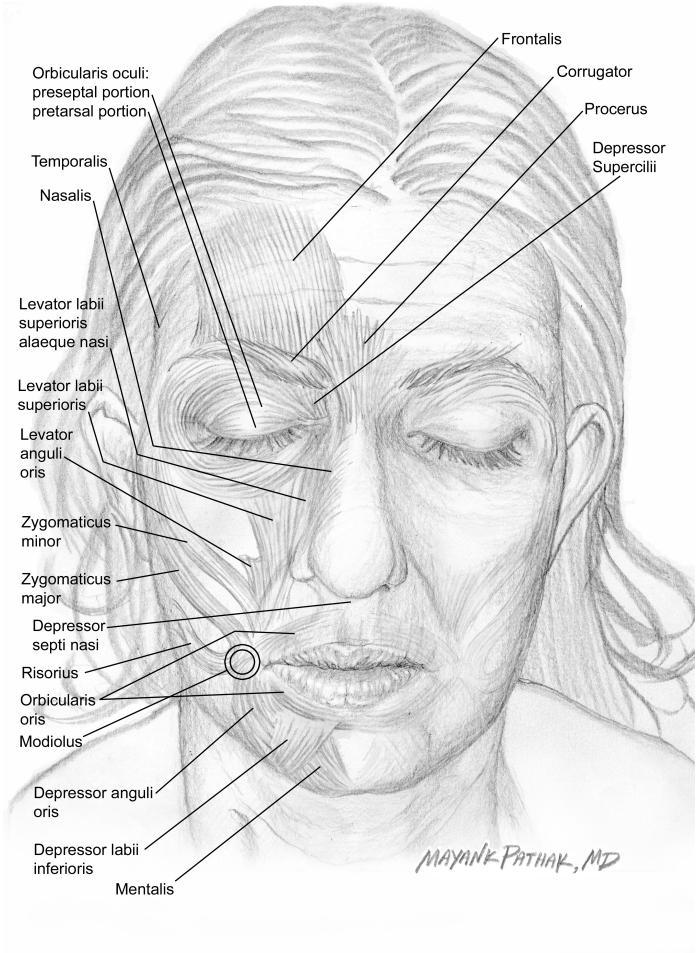
- Botox® approved by the FDA for glabellar rhytides in 2002
- Primary axillary hyperhidrosis in 2004.
- Chronic migraine in 2010
- Upper limb spasticity in adults in 2010
- Neurogenic detrusor overactivity in 2011
- Overactive bladder 2013
- Off-label use is widespread and includes tremor, anal fissure, achalasia, various conditions of pain, and others. Outside of the USA, there are at least 20 indications in 83 countries.

COSMETIC USES OF BOTULINUM TOXINS

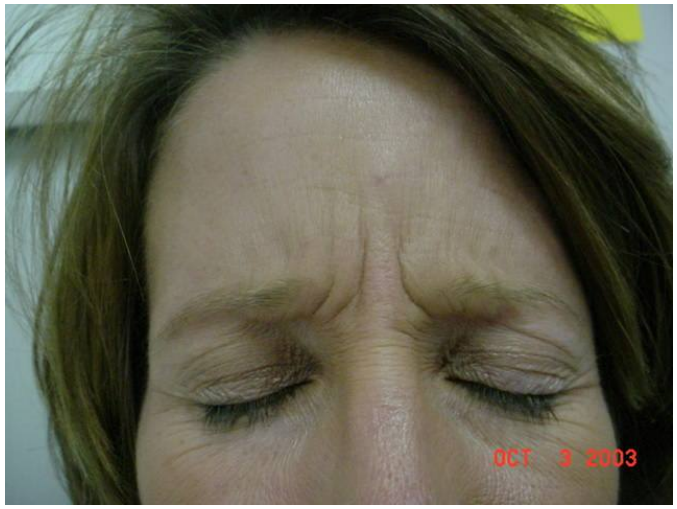
- The use of Botox® for wrinkles has been very popular and is perhaps the best known indication in the general public.
- In a 2007 study, patients reported looking 3 years younger than baseline 4 weeks after receiving BoNT to the upper face (Carruthers & Carruthers, 2007)

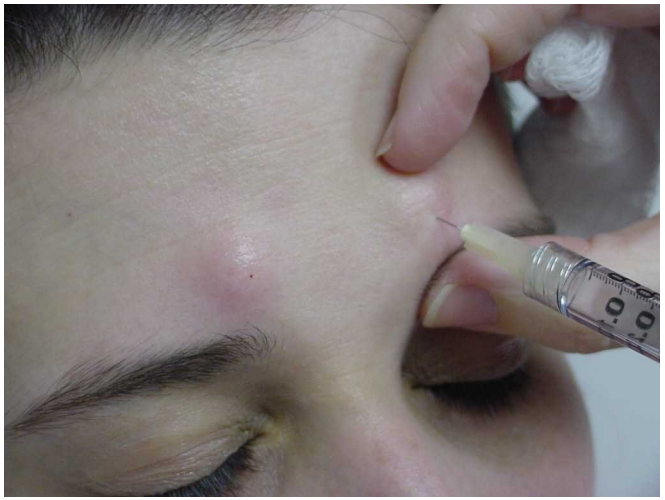
COSMETIC USES OF BOTULINUM TOXINS

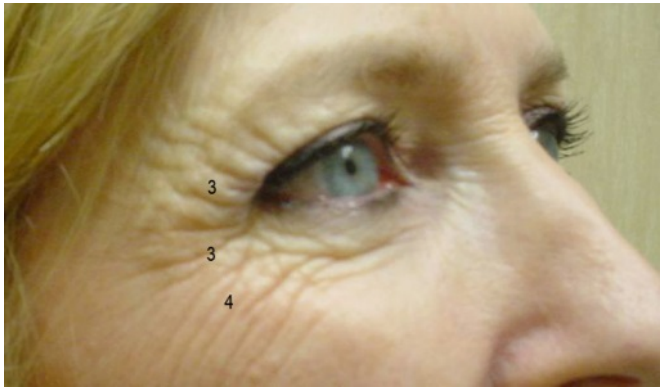
- The primary cosmetic use of BoTN-A relies on the relaxation of various muscles of facial expression.
- Many of these muscles have soft tissue attachments, investing in the dermis itself (e.g., the platysma), other muscles of facial expression (e.g., orbicularis oris to the risorius), or the superficial muscular aponeurotic system.
- The interconnectedness and the soft tissue attachments of many of these muscles differentiate them from the skeletal muscles which, by definition, have bony attachments.

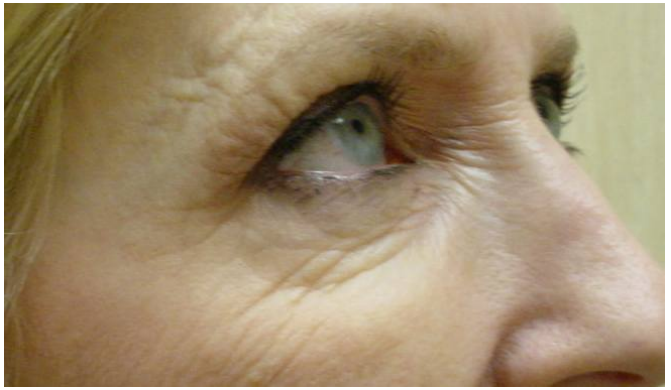


COSMETIC USES OF BOTULINUM TOXINS









PRIMARY AXILLARY HYPERHIDROSIS

- Hyperhidrosis may be defined as excessive sweating.
- It may be divided into generalized, regional and localized/focal types and, according to whether the cause is known or not, into primary and secondary forms.
- Three large randomized, placebo-controlled, double-blind studies and numerous open-label studies clearly document its effectiveness and safety of botulinum toxin in this indication.

PRIMARY AXILLARY HYPERHIDROSIS

- In a European study enrolling 320 patients, 94% of patients treated with 50 units (U) Botox® per axilla were treatment responders at week 4 (>50% reduction in sweat production from baseline gravimetric measurement) with an average reduction in sweat production of 83.5% (Naumann & Lowe, 2001).
- In a 12 month follow-up study, 207 of these patients received up to 3 further BoNT-A injections. Response rates and satisfaction with treatment remained consistently high with no diminution of effect and no confirmed positive results for neutralizing antibodies to BoNT-A with repeated treatments (Naumann et al., 2003).

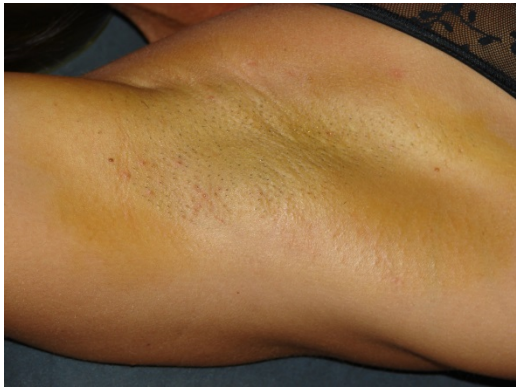
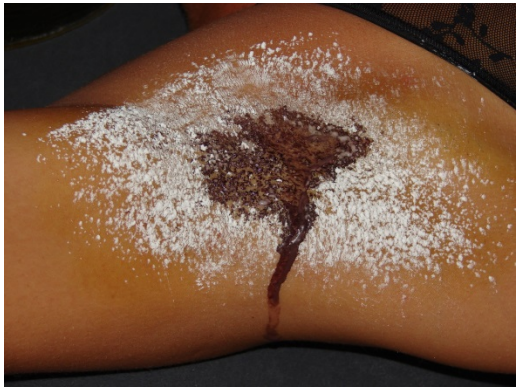
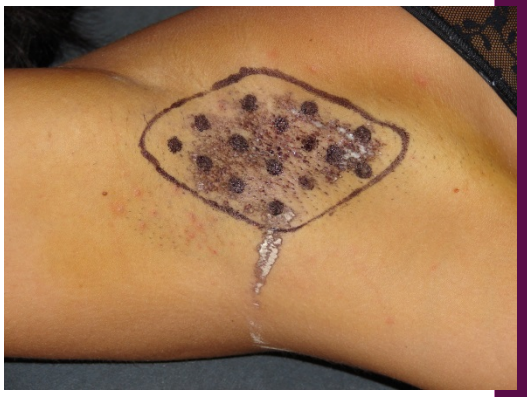
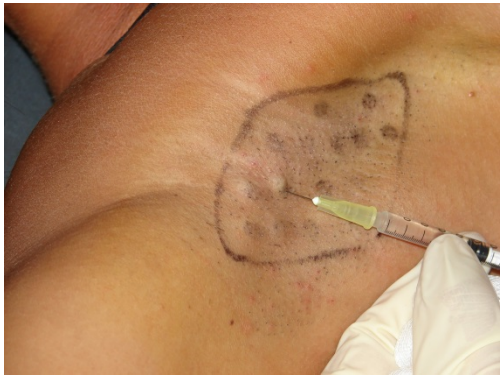
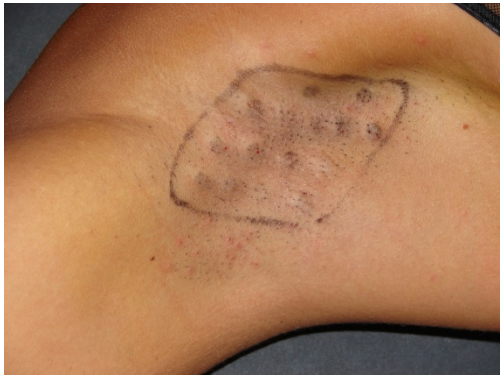
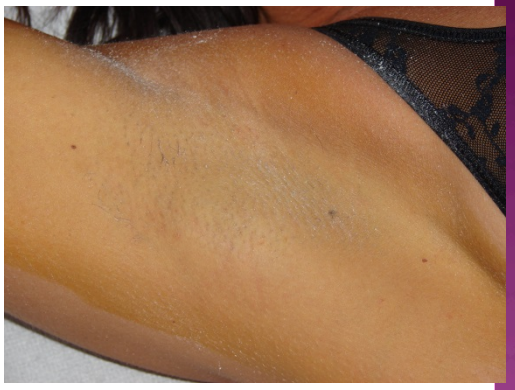
PRIMARY AXILLARY HYPERHIDROSIS

- Mean duration of benefit was about 7 months after a single treatment.
- Twenty-eight percent of patients did not require more than one injection, indicating a long-lasting benefit of at least 16 months.
- No major side effects occurred, with subjective increase in non-axillary sweating perceived by 4% of the patients being the most frequent complaint.
- BoNT-A treatment also markedly improved the quality of life of patients (Naumann et al., 2002).

PRIMARY AXILLARY HYPERHIDROSIS

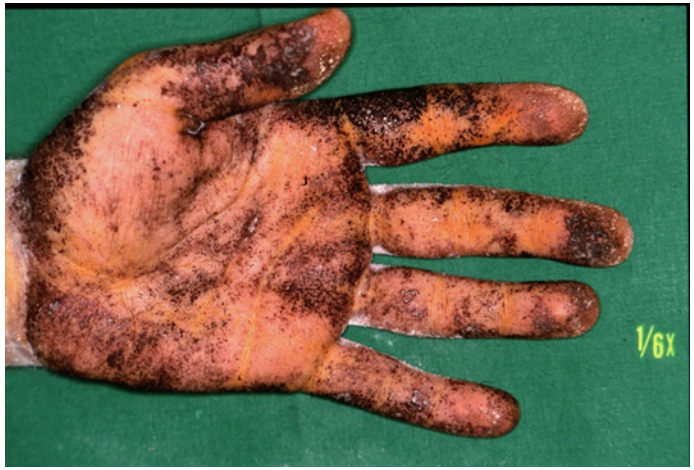
- In a multi-center North American trial in 322 patients comparing 50 U Botox® per axilla to 75 U Botox® per axilla and placebo, responders were defined as having at least a 2-grade reduction in their HDSS score.
- There was a 75% response rate in the treatment groups compared to a 25% response rate in the placebo-treated patients, but without significant difference between the groups treated with different Botox® doses (Lowe et al., 2007).
- Eighty to 84% of the treatment groups had at least a 75% reduction in sweat production, compared to only 21% in the placebo group.
- Median duration of the BoNT-A effect was again approximately 7 months.
- These studies brought about the license of Botox® for axillary hyperhidrosis in many countries worldwide.

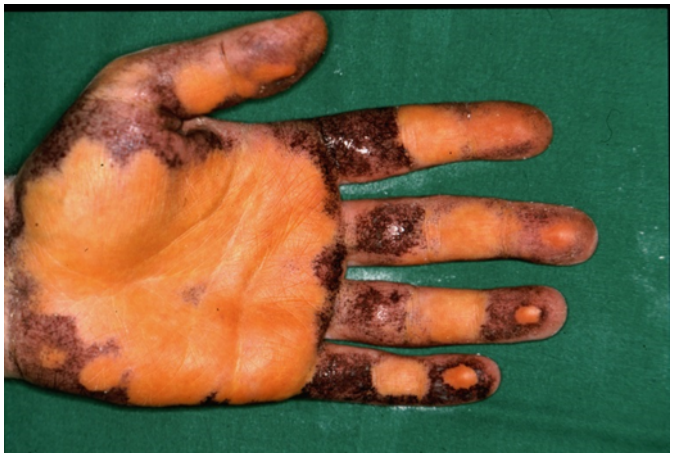
PRIMARY AXILLARY HYPERHIDROSIS

PALMAR HYPERHIDROSIS

- There are a number of smaller controlled and observational studies showing that BoNT-A (Botox®, Dysport®) is also a valuable treatment option in palmar hyperhidrosis (Saadia et al., 2001, Simonetta Moreau et al., 2003). However, treatment is more complex, injections are considerably more painful, higher doses are needed, and the effect is less pronounced and less long-lasting than in axillary hyperhidrosis.





PALMAR HYPERHIDROSIS

- Reduction or elimination of pain during palmar injections can be achieved by median and ulnar nerve blocks performed a few centimeters proximal to the wrist. Transient paresthesias and the potential risk of permanent nerve damage are major disadvantages.
- Cryoanalgesia with ice cubes, frozen gel packs, forced cold air, liquid ethylchloride or dichlorotetrafluoroethane (Frigiderm®) is preferred (Doft et al., 2012).
- Precooling of the hand in iced water.
- Topical lidocaine cream, vibratory anesthesia, intravenous regional anesthesia (Bier block), and general sedation to reduce or eliminate the pain.

CHRONIC MIGRAINE

- Migraine is a primary headache disorder characterized by enhanced sensitivity of the nervous system(3) associated with a combination of neurologic, gastrointestinal, and autonomic disturbances.
- It is estimated that 28 million Americans, including 18% of women and 7% of men, are afflicted with severe, disabling migraines.
- The association between BoNT use and the alleviation of migraine headache symptoms was discovered during initial clinical trials of BoNTA treatment for hyper-functional facial lines

CHRONIC MIGRAINE

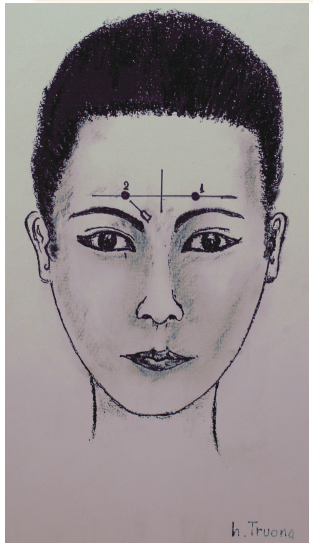
- Based on exploratory phase 2 CM studies the PREEMPT clinical program has established a successful modified follow-the-pain protocol treatment paradigm.
- OnabotulinumtoxinA (155 U) is administered as 31 fixed-site, fixed-dose injections across 7 specific head and neck muscle areas.
- Up to 40 U of additional onabotulinumtoxinA can be administered, using a follow-the-pain strategy, into the temporalis, occipitalis, and/or trapezius muscles, with a maximum dose of 195 U administered to 39 sites

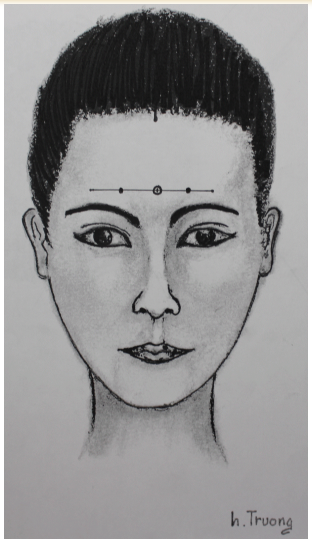
Table 26.1 OnabotulinumtoxinA dosing for chronic migraine by muscle

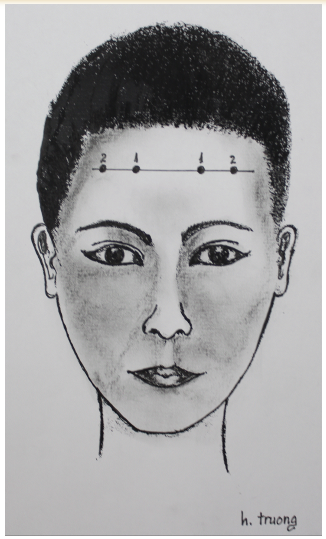
Head/neck area	Total dose (U [No. intramuscular injection sites[a]])	
	Minimum dose	Maximum dose
Frontalis	20 (4)	20 (4)
Corrugator	10 (2)	10 (2)
Procerus	5 (1)	5 (1)
Occipitalis	30 (6)	≤40 (5 U/site) (≤8)
Temporalis	40 (8)	≤50 (5 U/site) (≤10)
Trapezius	30 (6)	≤50 (5 U/site) (≤10)
Cervical paraspinal muscle group	20 (4)	20 (4)
Total dose	155 (31)	195 (≤39)

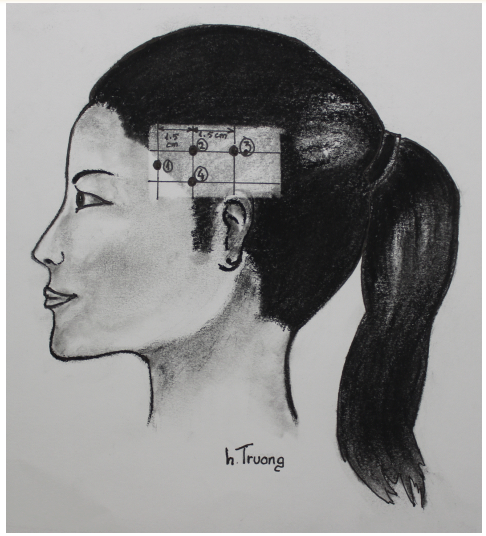
[a] Each intramuscular injection site received 0.1 ml (5 U) onabotulinumtoxinA.

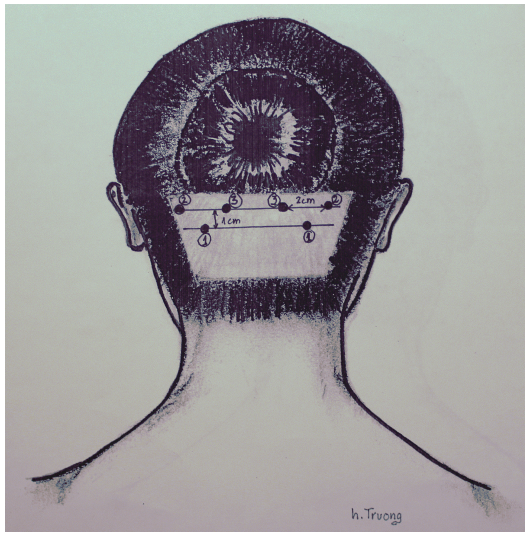
CHRONIC MIGRAINE

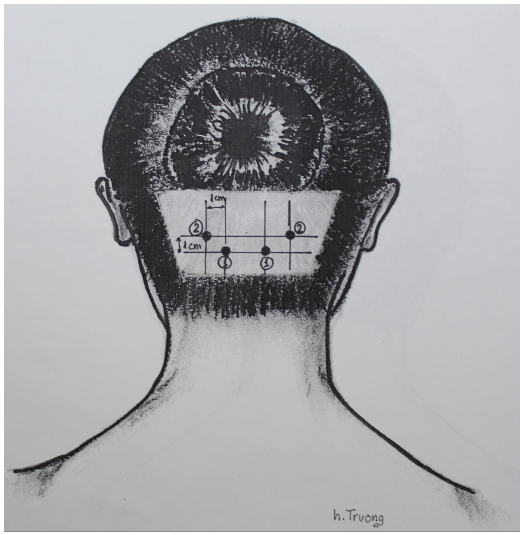


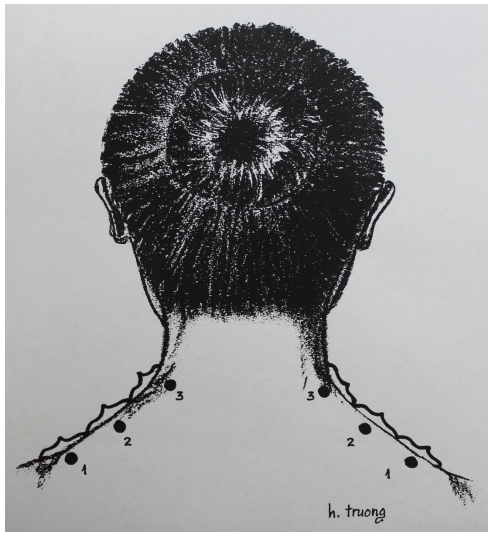












SPASTICITY

- Spasticity is characterized by increased muscle tone, exaggerated tendon reflexes, repetitive stretch reflex discharges (clonus), and released flexor reflexes (great toe extension; flexion at the ankle, knee and hip.
- Late sequelae may include contracture, pain, fibrosis, and muscle atrophy.
- Efficacy is best documented for the upper limbs
- Clinical experience showed a good safety profile both in the short (Naumann et al.2004) and in the long term use (Naumann et al. 2006).

SPASTICITY

INTRAMUSCULAR INJECTION OF BOTULINUM TOXIN FOR THE TREATMENT OF WRIST AND FINGER SPASTICITY AFTER A STROKE

ALLISON BRASHEAR, M.D., MARK F. GORDON, M.D., ELIE ELOVIC, M.D., V. DANIEL KASSICIEH, D.O., CHRISTINA MARCINIAK, M.D., MAI DO, B.S., CHIA-HO LEE, M.S., STEPHEN JENKINS, M.D., AND CATHERINE TURKEL, PHARM.D., FOR THE BOTOX POST-STROKE SPASTICITY STUDY GROUP*

European Journal of Neurology 2006, **13** (Suppl. 4): 35–40

ORIGINAL ARTICLE

Safety and efficacy of botulinum toxin type A following long-term use

M. Naumann[a], A. Albanese[b], F. Heinen[c], G. Molenaers[d] and M. Relja[e]

Neurol Sci (2005) 26:26–31
DOI 10.1007/s10072-005-0378-9

ORIGINAL

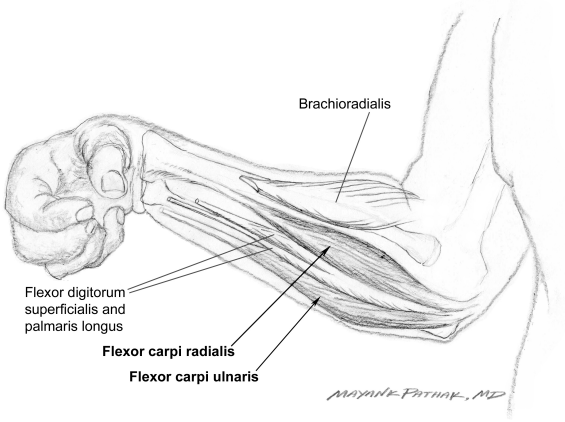
F. Mancini · G. Sandrini · A. Moglia · G. Nappi · C. Pacchetti

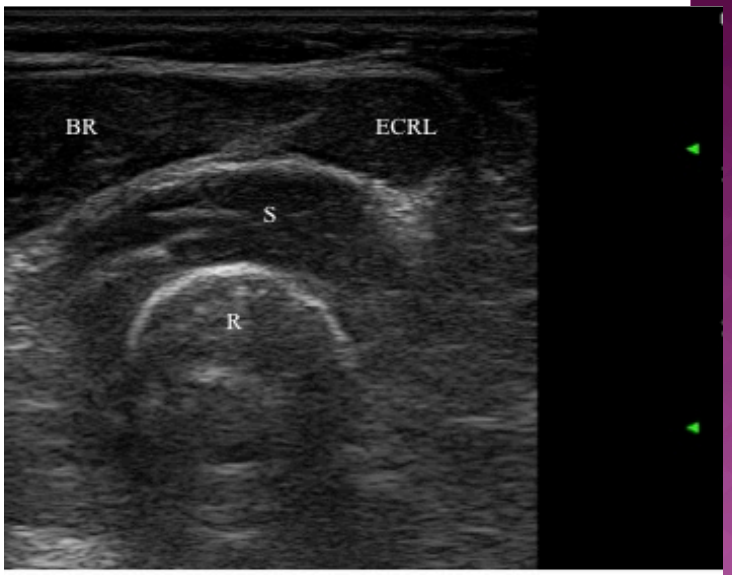
A randomised, double-blind, dose-ranging study to evaluate efficacy and safety of three doses of botulinum toxin type A (Botox) for the treatment of spastic foot

Received: 5 July 2004 / Accepted in revised form: 3 February 2005

SPASTICITY

- Injection with EMG guidance
- Injection with ultrasound



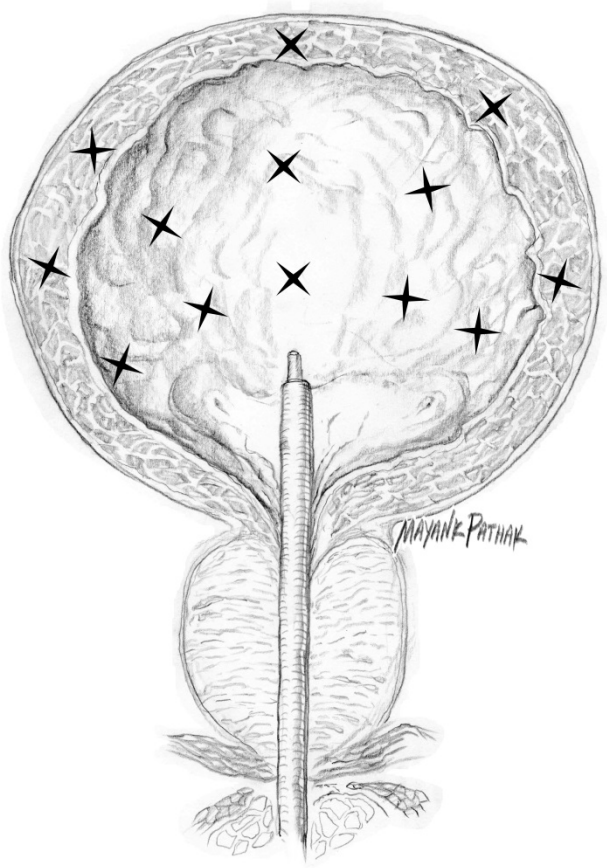


OVERACTIVE BLADDER

- The International Continence Society (ICS) report of 2002 defined the overactive bladder syndrome as urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of local pathological or hormonal factors.
- The prevalence in Europe and USA was estimated
  - 3% men 40-44 years of age
  - 9% women 40-44 years of age
  - 42% men >75 years of age
  - 31% women >75 years of age

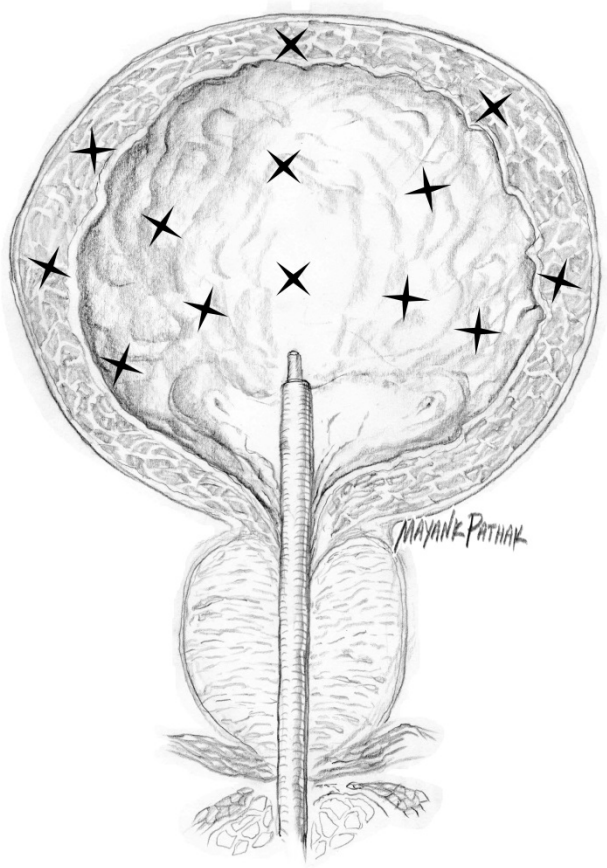
OVERACTIVE BLADDER

- Direct injection of BoNT into the detrusor muscle appears to ameliorate detrusor hyperreflexia in patients with spinal cord injury (Ginsberg, et al. 2012; Cruz, et al. 2011; Herschorn, et al. 2011).
- Injection technique consists of injecting mainly the detrusor and sparing the trigone using a rigid or a flexible cystoscope.
- A recent randomized study comparing trigone-sparing with trigone-including injections, showed better results in the latter group (Manecksha, et al. 2012).



OVERACTIVE BLADDER

- Injection doses varied between 100 and 300 (mouse) units of BoNT-A (Botox®) and 500 and 1000 units of BoNT-A (Dysport®) for neurogenic detrusor overactivity (NDO).
- Injection doses have varied between 100 and 300 units of Botox® and 300 to 1000 units of Dysport® for idiopathic detrusor overactivity (IDO).
- Mean duration of improvement has varied between 6 and 9 months with Botox and between 5 and 10 months with Dysport®.
- The continence improvement rate is 86.5% with Botox and 86% with Dysport®.
- No side effects related to the injection itself have been reported with the exception of a risk of urinary tract infections of 7.1% to 24%

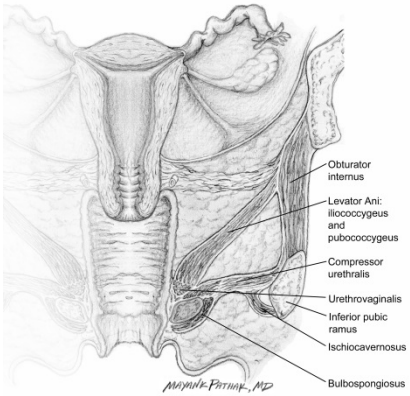


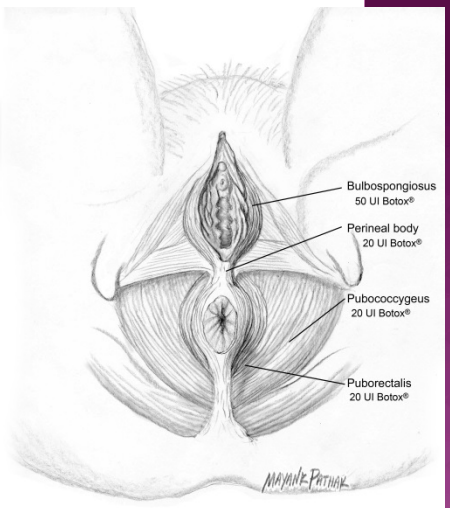
VULVODYNIA

- Vulvodynia is a chronic disorder in women defined as vulvar discomfort, most often described as burning pain
- characterized by provoked or unprovoked vulvar pain of varying intensity without obvious concomitant clinical pathology.
- Two subtypes of vulvodynia: generalized and localized.The latter is currently referred to as vestibulodynia or vestibulitis.
- 15-20% of the female population in the United States

VULVODYNIA

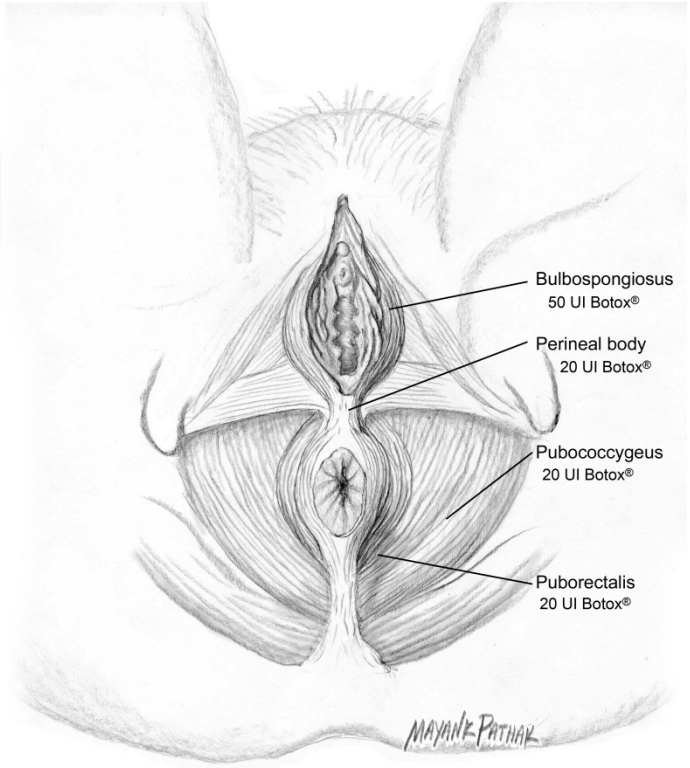
- Injection techniques with BoNT for vulvodynia range from 10-50 units (Botox®) and 150-400 units (Dysport®).
- Injection sites have included the anterior vaginal wall muscles, the puborectalis, pubococcygeus, perineal body, bulbocavernosus, and bulbospongiosus muscle.
- Studies have been mainly single or multiple case series with single or multiple follow-up injections. One study was controlled (Shafik & El-Sibai 2000), whether all other were prospective cohort studies or case reports.
- All studies showed improvement in most patients regarding pain, muscle spasm, quality of life, and sexual activity. Duration of effects lasted from 4 weeks to 2 years





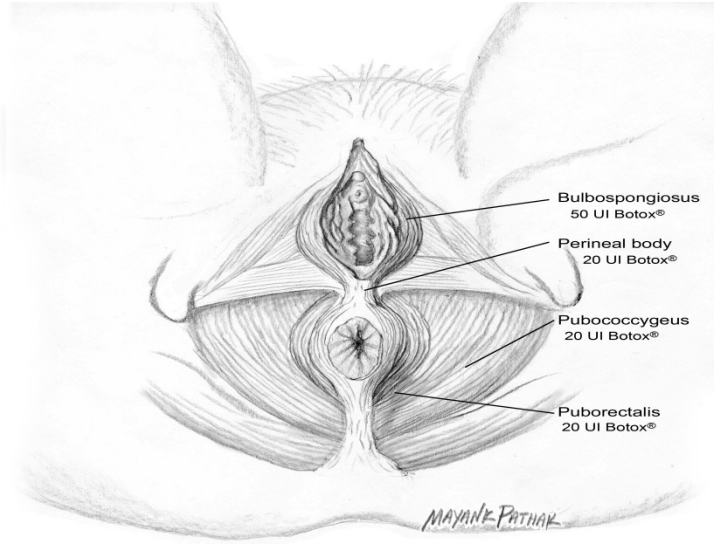
CHRONIC PELVIC PAIN

- Approximately 15-20% of women aged 18-50 years have chronic pelvic pain of greater than 1 year duration (Howard, 2003).
- Chronic pelvic pain may result from psychological disorders or neurological diseases both central and peripheral.
- Several of the most common disorders in women such as endometriosis, interstitial cystitis, irritable bowel syndrome, and pelvic inflammatory disease are causes of chronic pelvic pain.
- In men, chronic pelvic pain syndrome is an enigmatic medical condition, that has been classified as category III chronic pelvic pain syndrome or non-bacterial chronic prostatitis and, more recently, as Prostate Pain Syndromes (Fall et al., 2010.



CHRONIC PELVIC PAIN

- Patients with chronic pelvic pain may have generalized or localized pelvic pain, pain with intercourse, with ejaculation, after sexual intercourse, by both premenstrually and menstrually, and complain of voiding symptoms of frequency, urgence and nicturia
- Injection techniques with BoNT for chronic pelvic pain have ranged from 40 to 200 units of Botox®. Injection sites have included the puborectalis (20 to 50 Botox® UI), pubococcygeus (25 Botox® UI), the bulbospongiosus (25 Botox® UI), the perineal body (25 Botox® UI) and external urethral sphincter muscles.
- Electromyography was used in two studies to improve muscle localization. Two studies were randomised, placebo-controlled (Abbott et al., 2006; Gottsch et al., 2011), while the others were prospective cohort studies or case series.



- All studies showed improvement in most patients regarding pain, spasm, quality of life, and sexual activity.
- Duration of effect was 12 weeks to 1.5 years.

BENIGN PROSTATIC HYPERPLASIA

- Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate and is regarded as a major cause of bladder outlet obstruction.
- The pathophysiology of BPH may involve a dynamic component that reflects the smooth muscle tone within the gland and a static component that is related to the mass effect of the enlarged prostate.
- Botulinum toxin may have an effect on both components by relaxing smooth muscle and causing atrophy of the glandular tissue.
- There have been a few studies on the use of BoNT in humans. Most studies were case series, while one was a double-blind, placebo-controlled randomized study (Maria et al. 2003).
- In all studies patients showed improvement in mean prostate volumes, symptom scores, quality-of-life measurements, post-void residual volumes, peak flow rates, and serum prostate-specific antigen concentration (Silva et al., 2008; Silva et al., 2009; Brinsinda et al., 2009; Maria et al. 2003; Crawford et al. 2011). Onset of effects was within 1 week of injection and duration was from 3 to 9 months.

BENIGN PROSTATIC HYPERPLASIA

- One hundred to 300 units of BoNT-A (Botox®) were injected at two to ten sites with a 4-20 cc dilution factor.
- Botulinum toxin was injected into the transition zone at the lateral lobes and median lobes of the prostate or both lateral lobes of the prostate.
- Injections were done via rectal utrasound, transrectal ultrasound or via cystoscope. Injections were done without sedation or anesthesia or under light intravenous sedation or general anesthesia.
- No meaningful difference was observed between using 100 or 300 Botox units (Crawford et al. 2011).