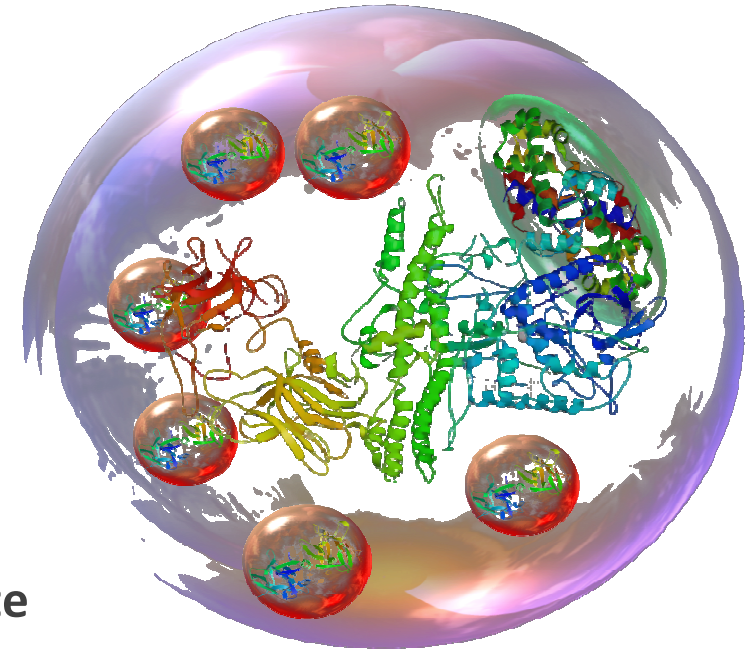
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Innovazione e
Trattamenti Mini Invasivi in Proctologia
Cona, 22 settembre 2012

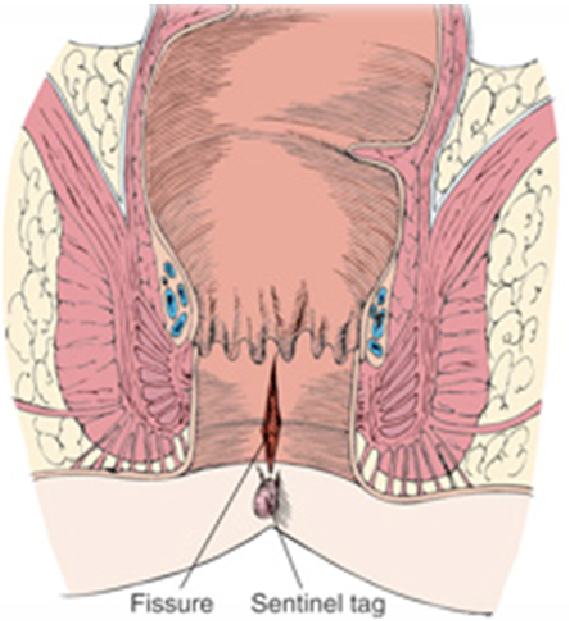
La tossina botulinica nel trattamento della ragade anale



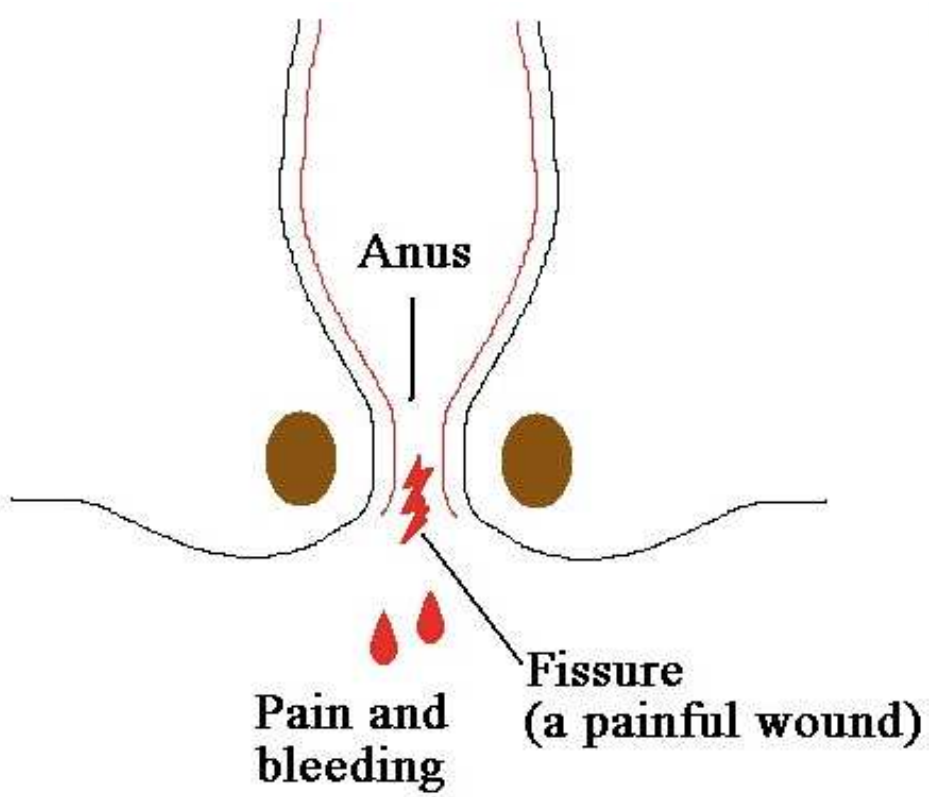
Valeria Tugnoli, Elisabetta Sette

U.O.S. di Neurofisiologia
D.A.I. Neuroscienze-Riabilitazione – Ferrara
v.tugnoli@ospfe.it

Anal Fissure

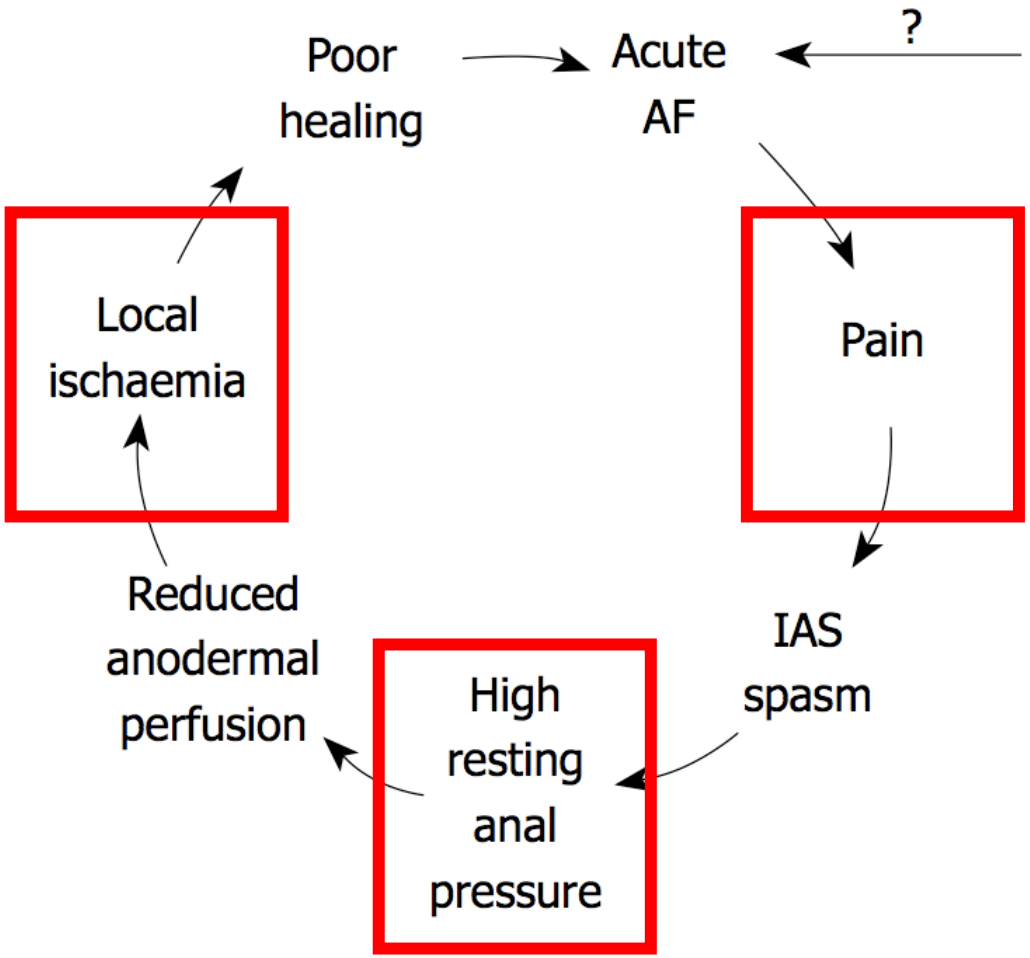


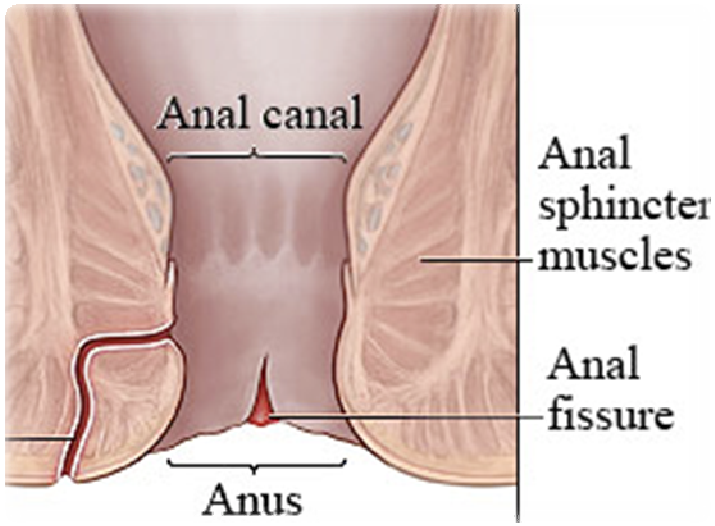
- *A linear ulcer of the anoderm, distal to the dentate line, generally located in the posterior midline*
- Chronic fissures are characterised by a hypertophic anal papillae, anal spasm, and/or fibrosis of the inner sphincter muscle
- At 6 o'clock in 80-90% (any other position need further investigation as to the underlying Crohn's disease, anal intercourse, sexually transmitted disease, or anal carcinoma)
- **2009** Annual Report prepared by the SICCR (Italian Society of Colorectal Surgery) →**5,199** pts were observed for anal fissure, **37%** of whom underwent surgery



- Extremely painful during defecation; the pain is cramp-like and may persist for hours (chronic anal fissures → less intense during defecation, but increases after that)
- Increased intraanal pressure at rest might contribute to an ischemic state of the anal sphincter muscles

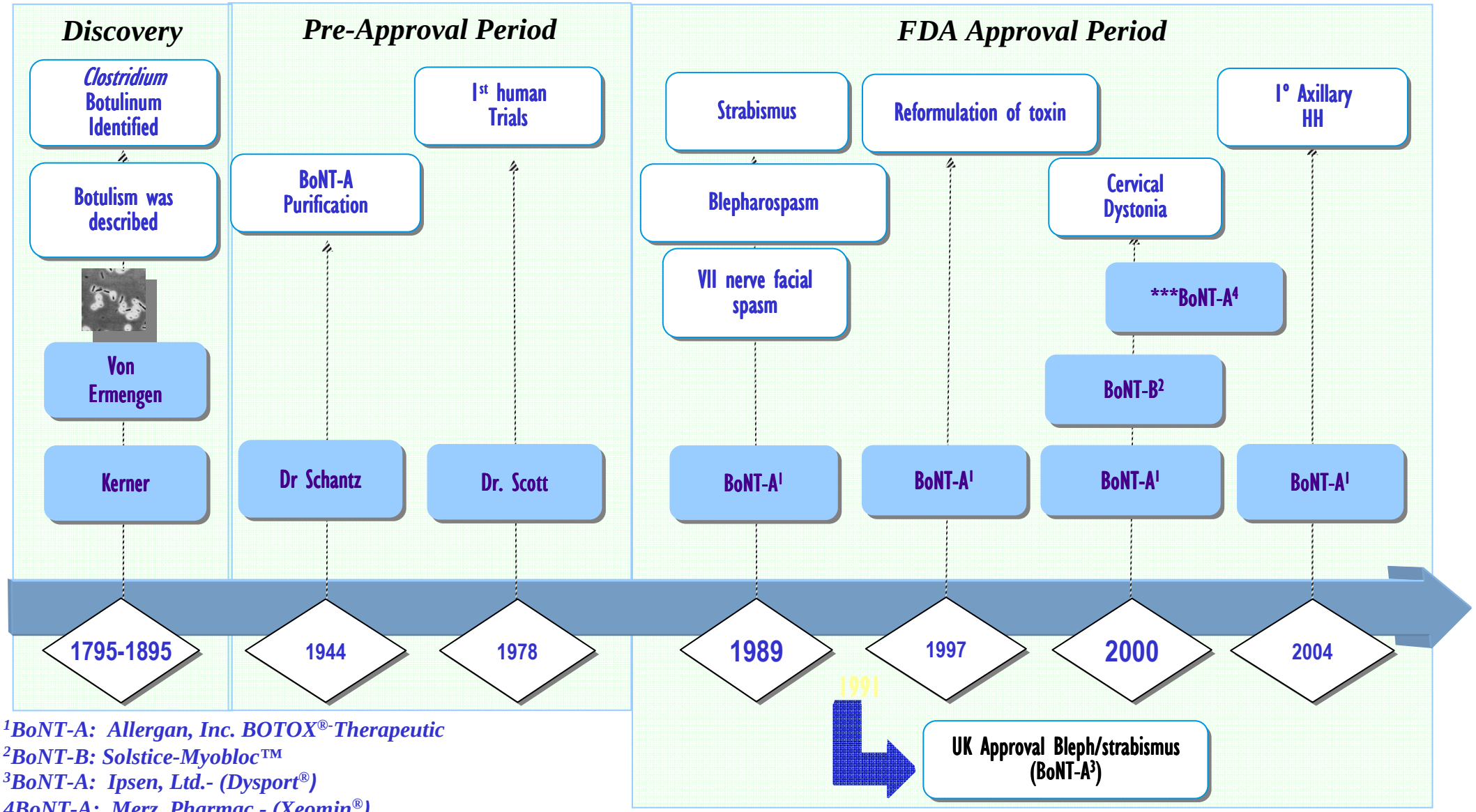
Devil's circle of spasm and pain



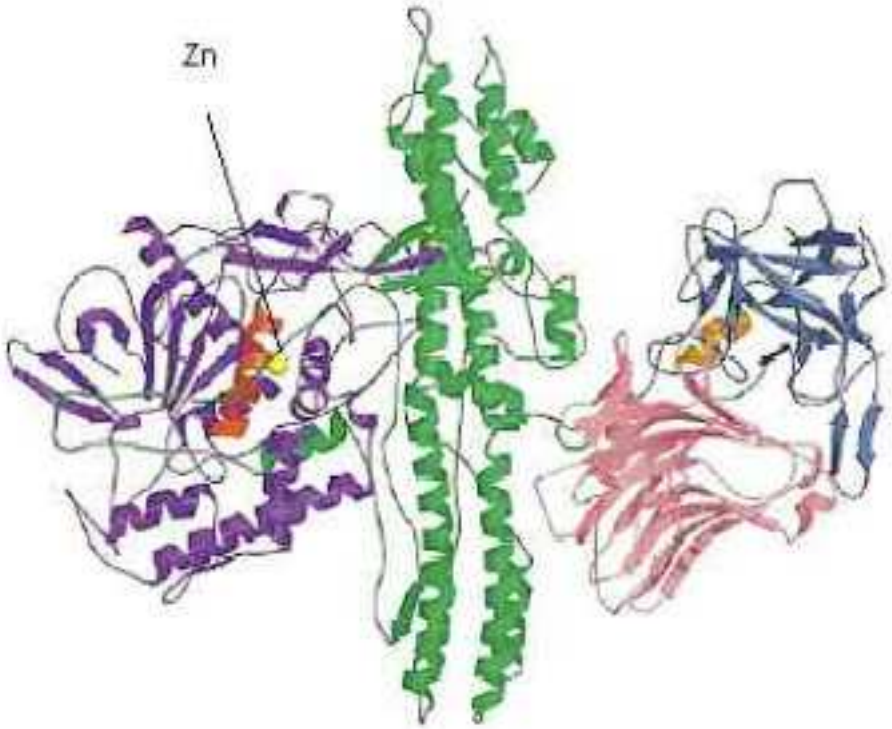


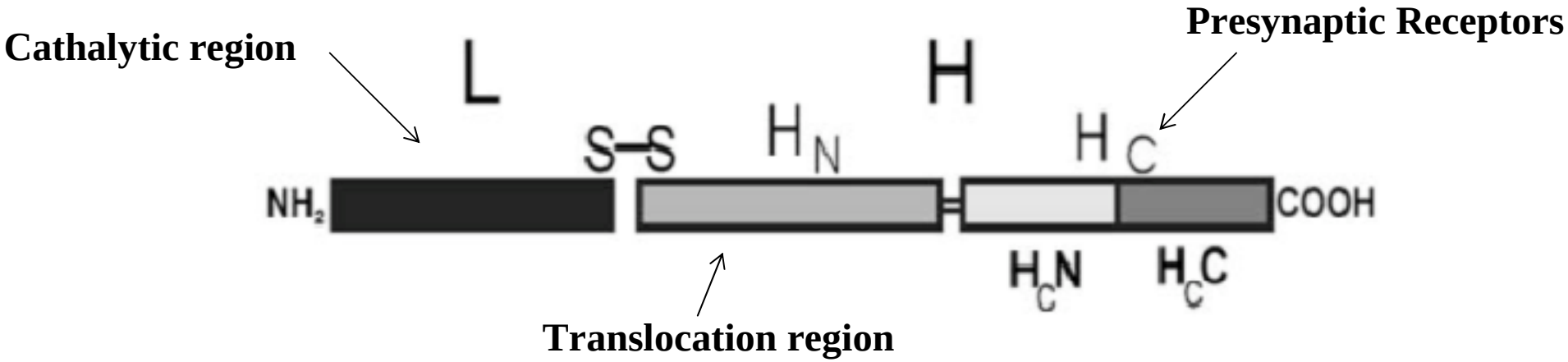
The **treatment goal for BTX** is the interruption of the internal sphincter spasm and thereby, the ischemic state.

Timeline of Botulinum Toxin Therapeutic Development

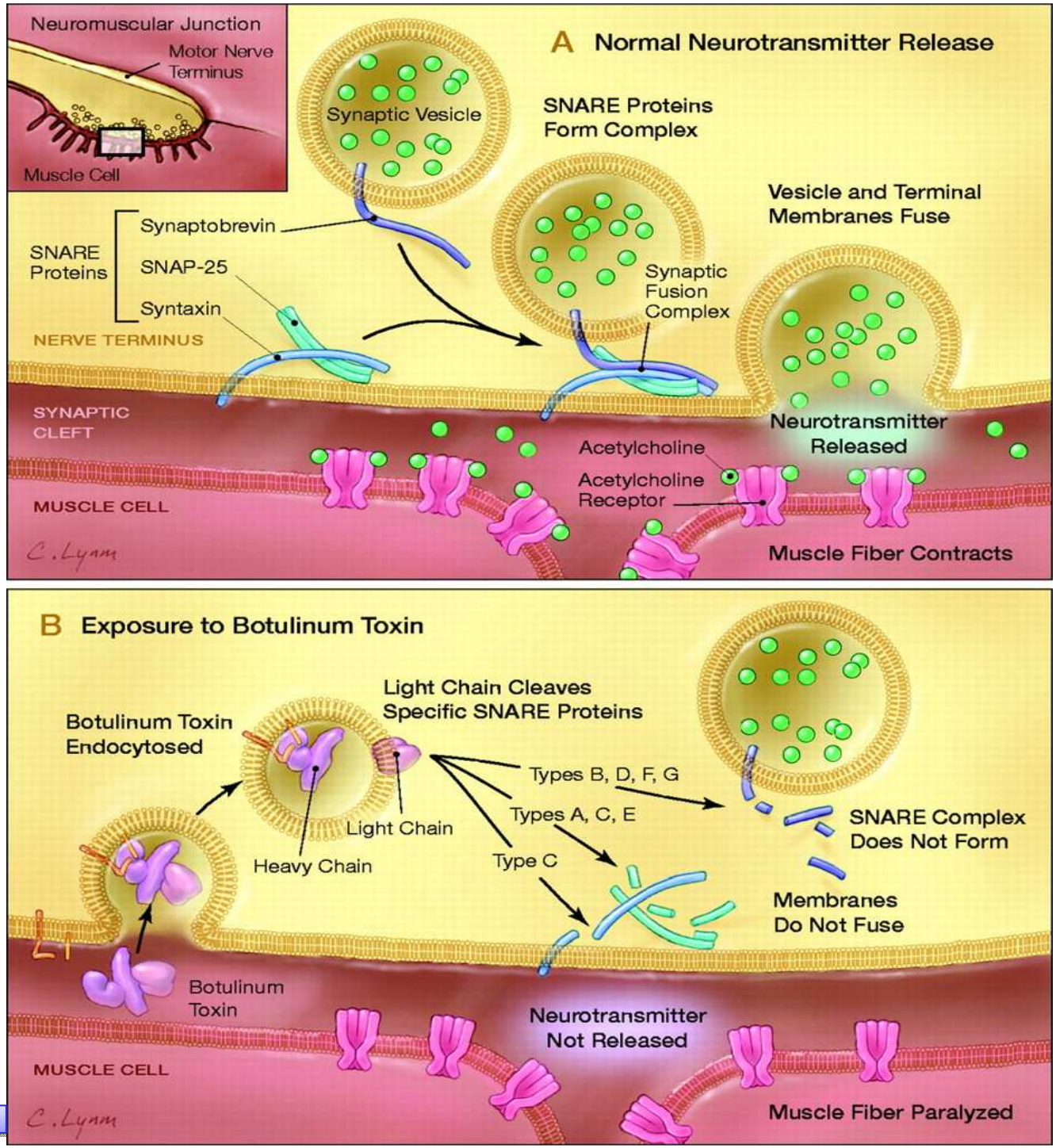


[1]*BoNT-A: Allergan, Inc. BOTOX®-Therapeutic*
[2]*BoNT-B: Solstice-Myobloc™*
[3]*BoNT-A: Ipsen, Ltd.- (Dysport®)*
4*BoNT-A: Merz, Pharmac.- (Xeomin®)*


Zn


Cathalytic region
Presynaptic Receptors
L
H
S–S
H_N
H_C
NH_2
COOH
H_CN
H_CC
Translocation region

Blocco esocitosi



Arnon, S. S. et al. JAMA 2001;285:1059-1070.

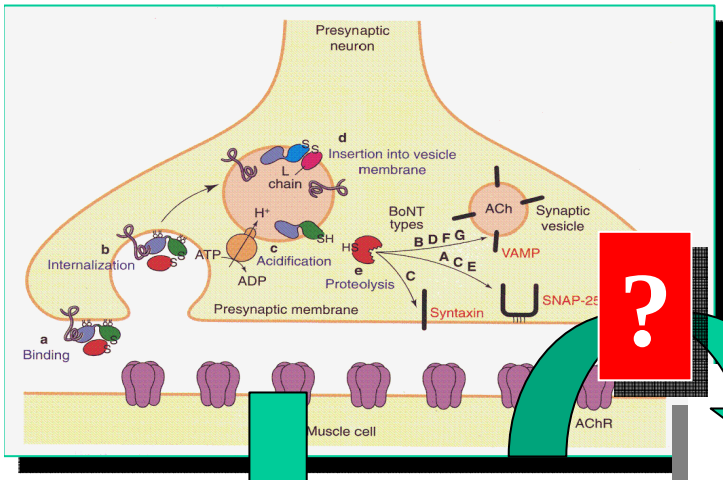
- Test del Frontale

Ferrara 22 settembre 2012

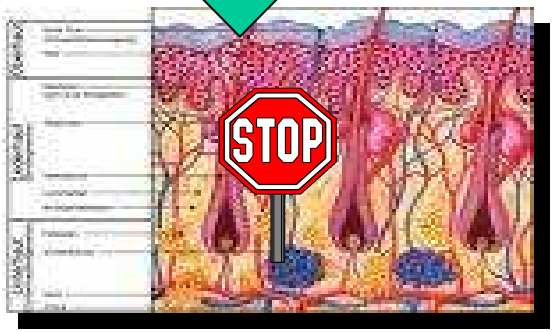
Botulinum neurotoxins: mechanism of action and therapeutic applications

Is time to challenge this "ancient" chapter

D.De Grandis, V.Tugnoli, C.Montecucco 1995



?



Peripheral Nervous System

Central Nervous System

Peripheral Sensitization

Glu, Sp, CGRP, NA, NGF
BK, PGs, HA, 5-HT, H^+
Adenosine, NO

Botulinum Toxin

C-fiber

Impulses

Aβ fiber

Dorsal root ganglion
Trigeminal ganglion

Central Sensitization

Glu
Sp

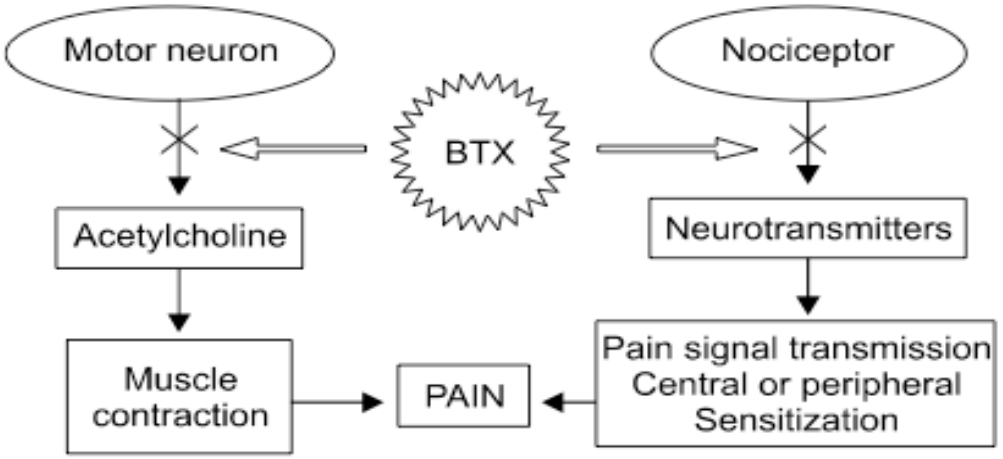
Wide range dynamic neuron

Nucleus Trigeminal Caudalis

BoNT and Pain: effects on *Muscular* and *Non Muscular-related* events

1. Inhibition of the **Vicious Circle** muscle contraction-pain-muscle contraction
2. Decompression of **nociceptive intramuscular fibres**

- Block of surface expression of Vanilloid receptors TRPV1 (Morenilla-Palao '04)
- Inhibition of neuropeptide release from primary sensory neurons (Glu (Cui'00,'02),CGRP(Morris'01, Durham'04), Subst.P(Purkiss ''00), Norepinephrine (Shone'02), ATP(Smith Hannover '02)), Trigeminal Ganglia (infraorbital nerve constriction IOC, Kitamura '09)
- Reduction of peripheral sensitization (Formalin-pain models) and of the related central sensitization (c-Fos,Wells '01)
- Inhibition of Autonomic System and of Inflammatory cells (mastzellen)?



Casale R, Tugnoli V 2008

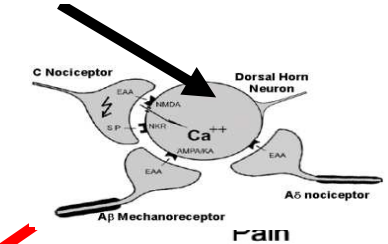
Pain 130 (2007) 76–83

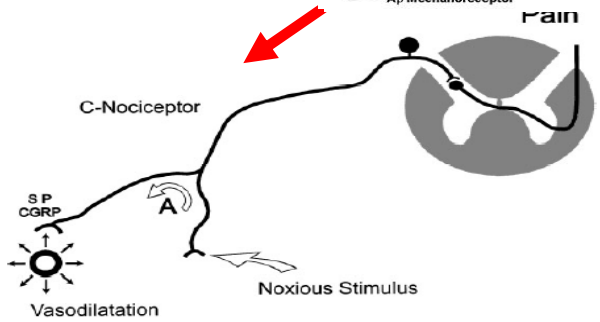
PAIN

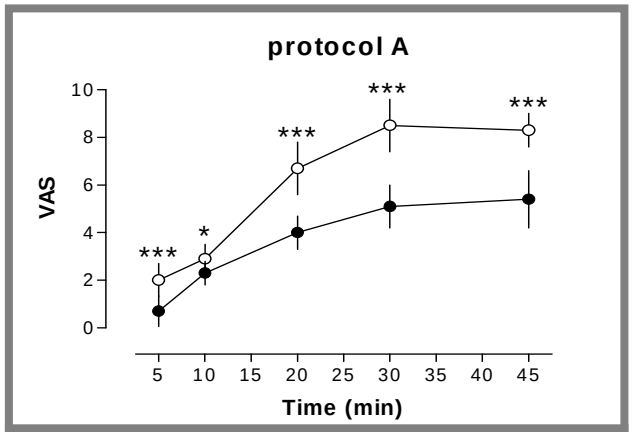
www.elsevier.com/locate/pain

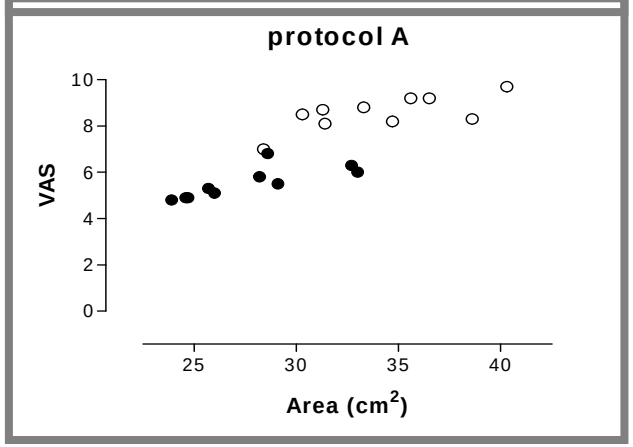
Botulinum Toxin type A reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin

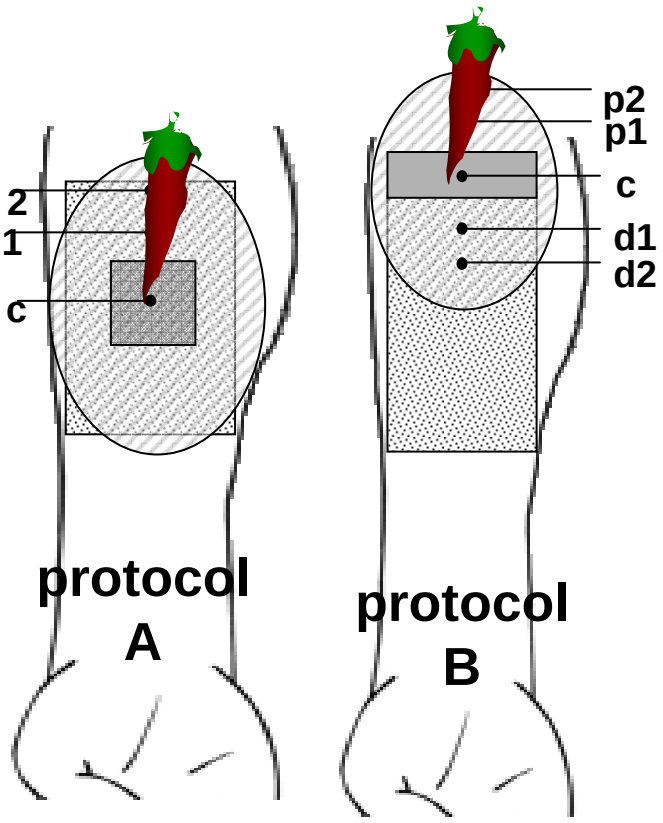
Valeria Tugnoli [a,*], Jay Guido Capone [a,b], Roberto Eleopra [a], Rocco Quatrale [a], Mariachiara Sensi [a], Ernesto Gastaldo [a], Maria Rosaria Tola [a], Pierangelo Geppetti [b,c]

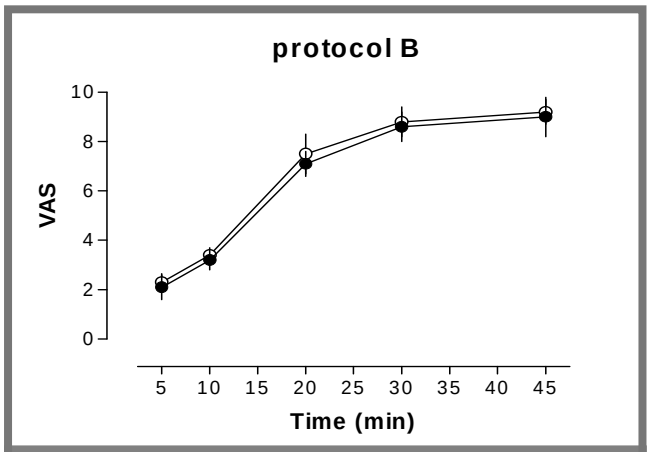


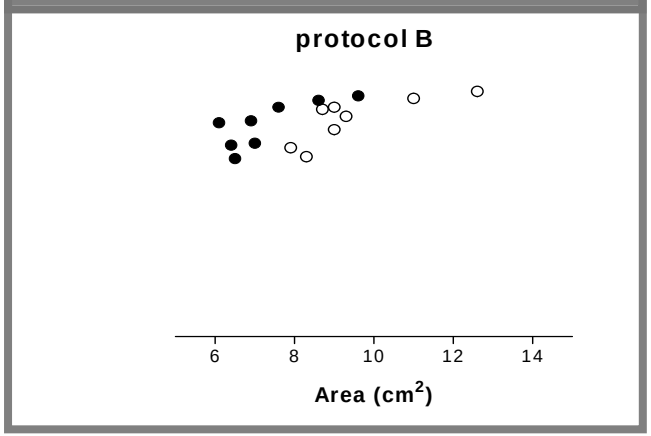












Ferrara 22 settembre 2012

- BTX for the first time in 1993
- Nelson's meta-analysis (2006) → overall response rate 55%GTN, 65%BTX and 85%
- The 3rd revision of the American Society of Colon and Rectal Surgeons' (ASCRS) guidelines (2010) → BTX injection allows healing in 60%-80% of fissures and higher rates than placebo with recurrence in up to 42% of cases

ANAL FISSURE → BoNT Treatment

Authors/year Low dose	BoNT UI/ Pts n°	%Complete Healing		Authors/year High dose	BoNT UI/ Pts n°	% Complete Healing
Gui et al 1994	15UI/10 IAS	90		Siproudhis et al 2003	100UI/22	**32**
Jost *et al 1997*	2,5UI/100 EAS	82		Kinney *et al 2006*	100UI/22 IAS	91
Minguez *et al.1999*	21UI/19 IAS	90		Tranqui et al 2006	100UI/50 IAS	**94**
Brisinda et al 1999	20UI/25 IAS	96		Valizadek et al 2012	50UI/50 IAS	44(1mo) 88(6mo)
Fernandez *et al 1999*	40UI/76IAS	67				
Maria et al 2000	20UI/25 IAS	**100**				
Lysy et al 2001	20UI/15 IAS	60				
Madalinski et al 2001	25UI/14 EAS	54				
Brisinda et al 2002	30UI/75	96				
Lindsey *et al.2003*	20UI740	**43**				
Giral *et al 2004*	30UI/10 IAS	70				
Wollina et al 2002	25UI/5 EAS	100				

Authors/years	Study	Pts n°	BoNT	Healing % (mo)
Maria et al 1998	Double arm, prospective, randomised	30	20UI	73,3% (2mo)
Lindsey et al 2003	Single arm, prospecitive randomised	40	20 UI after GTN 0,2% for 8 wk)	43% complete 12% sympt resolution 18% symp improvement 27% surgery
Brisinda et al 1999	Dual arm, prospective randomized	50	20UI vs GTN for 8 wks	96% (2mo) GTN 60%
Jones et al 2007	Dual arm, prospective, randomised, non-controlled	30	25UI+GTN vs 25UI alone	100% (2mo) 27%

- In this update (2012) **77RCTs** studies including **5031** participants
- 17 agents were used (nitroglycerin ointment (GTN), isosorbide mono & dinitrate, Botulinum toxin (Botox), diltiazem, nifedipine (Calcium channel blockers or CCBs), hydrocortisone, lignocaine, bran, minoxidil, indoramin, clove oil, L-arginine, sitz baths, sildenafil, “healer cream” and placebo) as well as Sitz baths, anal dilators and surgical sphincterotomy

- **Botox** was equivalent to GTN (**48,9%**) in efficacy with fewer adverse events.

- No medical therapy came close to the efficacy of surgical sphincterotomy, though none of the medical therapies in these RCTs were associated with the risk of incontinence.

Non surgical therapy for anal fissure (Review)

Nelson RL, Thomas K, Morgan J, Jones A

Ferrara 22 settembre 2012

MARKET BONT FORMULATIONS	**BOTOX®** **OnabotulinumtoxinA** **(Allergan Inc.; Irvine, CA) 19**	**MYOBLOC®/NEUROBLOC®** **RimatobotulinumtoxinB** **(Solstice Neurosciences: South San Fra) 2000**	**DYSPORT®** **AbotulinumtoxinA** **(Ipsen LTD; Berkshire, UK) 1991**	**XEOMIN®** **IncobotulinumtoxinA** **(Merz Pharmaceutical, Germany) 2005**
	100 UI BoNT/A **900-kd (LL)** **purified** neurotoxin complex, vacuum dried pH 7,4	5000 UI/ml BoNT/B **700-kd** **injectable** solution **pH 5,6**	500 UI BoNT/A A **300-500 k-d (M-L)** toxin-hemagglutinin complex, frozen dried pH 7,4	100 UI BoNT/A **150 k-d** **without** hemagglutinin complex pH 7,4
	5 ng protein	**55 ng protein**	**4,3 ng protein**	**0,6 ng protein**
	Polvere soluzione iniettabile id/im	Doesn't require reconstitution	Polvere soluzione iniettabile sc/im	Polvere soluzione iniettabile id/im
	2-8℃ o congelatore ≤ -5℃	2-8℃	2-8℃	**≤25 ℃**

VISTABEX®
Uso estetico

Anal Fissure → Off-label use, written consent obtained, drug cost not refoundable by SSN

Controindications

- **Absolute**
- *Gravidity and lactation*
- *Haemophilia and risk of bleeding*

- Myasthenia gravis, LES
- ALS
- Allergies against BoNT preparate
- Simultaneous or concommittent use of drugs such as aminoglycoside antibiotics (streptomycin, kanamycin, gentamycin, neomycin,spectinomycin etc.)

Relative

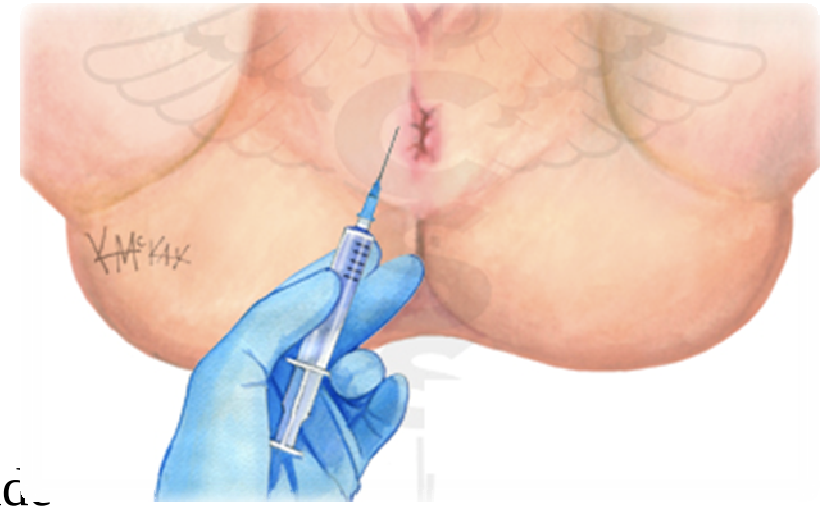
- *Noncompliance*

- Fluoride infections
- Severe smokers (healing impaired, interference with clotting)

BoNT preparation

- Dose
  - Low dosage (20-30UI) or high dosage (50-100 UI)
- Dilution:
  - The vials have to be resolved with sterile NaCl solution
- Needle
  - 27–32 gauge to minimize pain and bleeding

BoNT administration



- Injection should be done with the patient lying on one side
- An intramuscular injection is performed after local anhesthesia and disinfection
- Injections into both sides, along anal fissure margins, **at a distance of 1–2 cm** as fissure-associated ischaemia will prevent diffusion
- Site
  - **Internal** (doctor has to put 2 fingers in ano for the exact localization of the needle. This technique causes more pain for the patient and also carries the risk of needle stick injury for the doctor) **+ external** sphincter muscles (no needle risks).
  - **External** sphincter muscle alone.
  - As the internal sphincter is also involved in the pathophysiology of anal fissures, injection into only the external sphincter may not be fully effective in releiving the spasm.
  - BTX shows a **three-dimensional diffusion** of about 2 cm, which is considered adequate to reach the internal sphincter as well.
  - Along **the anterior** midline, are also effective.

Outcome

- The earliest effect is the antipruritic effect. It is important to note that fissure healing often takes more time than pain relief.
- The healing rates (≤ **6** mo) are **60–90%** and partial responses are seen in many patients.
- Long-term outcomes **(>12** mo) show complete healing rates of about **50%**
- The relapse rate →**35%**, with **7%** eventually treated by surgery
- Nonresponders are rare (< 5%) resulting mostly due to incorrect technique and/or diagnosis
  - The fibrosis may reduce the compliance of the internal sphincter, limiting diffusion of BoNT; may also destroy the myenteric nervous fibers, located between the circular and longitudinal smooth muscle layers → possible **role of Neurophysiology**

Adverse Events

- The identified complications following BTX are relatively benign.
- They may be subdivided into obligatory(1) and facultative (2) side effects.

1) relates to excessive weakness of AS (sphincter manometry after BTX injection has demonstrated a lowering of resting intranal pressure) → transitory incontinence for flatus (10-18%) or faeces (5-10%) and perianal thrombosis (1,1-19.2%) or hematoma (Maria et al 1998, 2002)
2) Facultative side effects related to BTX spreading from the target tissue to distant territories by hematogenic diffusion → flu-like syndrome (3%); subcutaneous infections (Minguez et al 1999), epididymitis was only incidental

- **All the identified side effects are transient and completely reversible**

Adverse Events

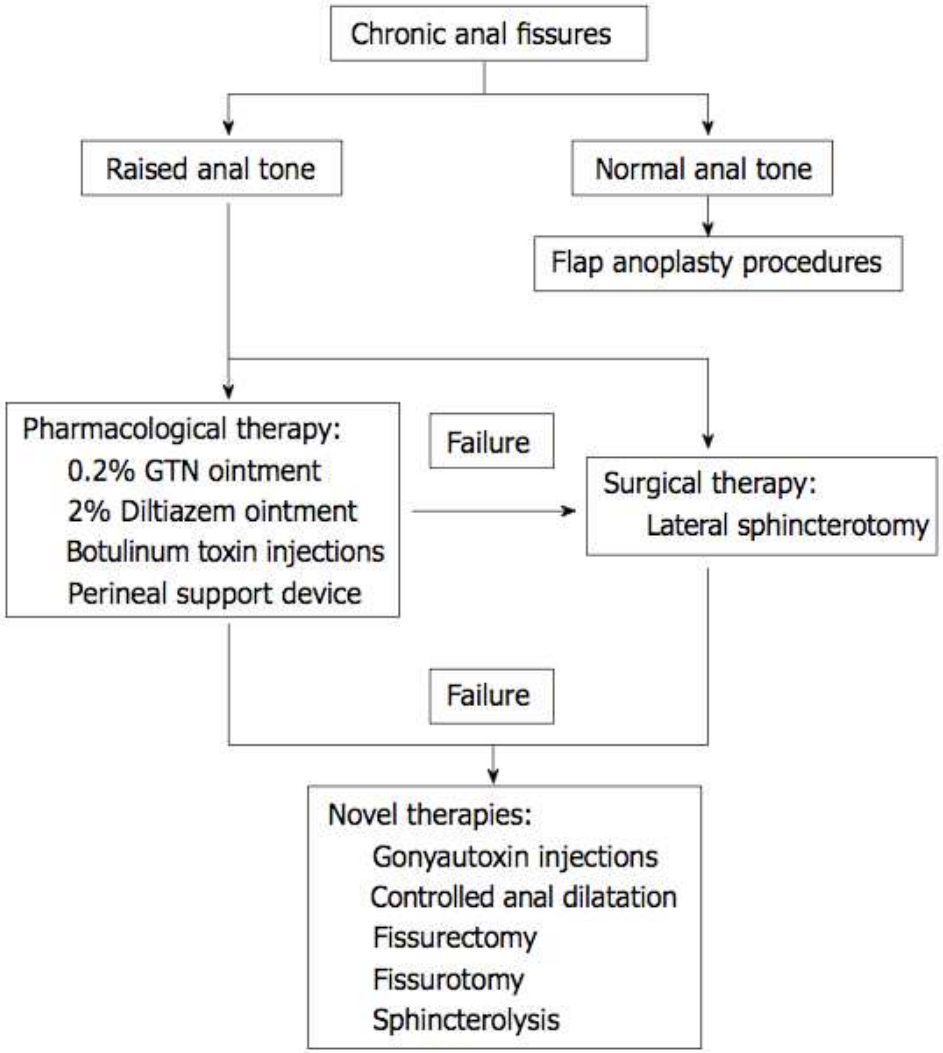
Authors/year	BoNT UI/ Pts n°	% Adverse Events
Maria et al 1998	20UI / 30	0
Lindsey et al 2003	20UI / 40	18% Minor incontinence-resolved
Brisinda et al 1999	20UI / 50	No bleeding
Jones et al 2006	25UI / 30	Transient incontinence
Arroyo et al 2005		6% Transient incontinence
Jost et al 2005		Perianal thrombosis (1 pt)
Radwan et al 2007		Transient faecal soiling (1 pt)
Mallo-Gonzales et al 2008		Necrotizing fasciitis in a 77-year-old male with diabetes mellitus

Criticisms

- Locating the drug
- Nonstandardized dose (Jost WH 1997), smaller doses of BTX may be less successful than a higher dose, but the optimal dose of BoNT has not been established
- Not well-defined injection site
  - different injection sites (anterior vs posterior IAS, EAS vs IAS, one site vs bilaterale) induce variable decreases in resting pressure and different rates of clinical outcome. (Minguez et al.1999; Maria et al 2000)
- Higher cost of treatment (Essani et al 2005)
- High percentage of recurrence (35–55% at 3–4 years) (Arroyo et al 2005)

Algorithms

- GTN ointment → BoNT → LIS
  - 7th United European Gastroenterology Week in 1999
  - *the New England Medical Journal 1999*
  - *Essan et al 2005* → ***88% of patients could avoid surgery and assessed the algorithm as highly cost-efficient***
- Higher doses of BoNT (50 or 100 UI of Botox) + GTN (Madalinsky 2001,Lindsey 2003)
- Higher doses of BoNT + fissurectomy (Madalinsky 2011)
- **ASCRS** provide a strong recommendation for LIS as the therapy of choice (grade 1a evidence), **BoNT non-operative treatment** should usually be considered as a first step in CAF therapy (**grade 1b recommendation**)
- **AIFA 2009**: GTN ointment; Surgical option: open or closed lateral internal sphincterotomy; Anoplast; BoNT and dilatations is not currently considered a suitable treatment



BoNT treatment vs lateral internal sphincterotomy (LIS) and fissurectomy (F)

- In PubMed and Embase (January 1993 - January 2011), 7 studies (539 patients)
- LIS →higher healing rate, less recurrence rate, but higher complications and faecal incontinence rate (Sajid et al)
- F+BoNT→ 79-93% success rate, excellent and safe procedure, low morbidity, high healing rate (Scholz et al, Brisinda et al, Lindsey et al 2004)

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Take home message

- ✓ BoNT is a useful, safe and effective treatment for anal fissures.
- ✓ The effect is dose-dependent and technique-dependent.
- ✓ It doesn't cause permanent AE
- ✓ It's more convenient than surgery as first line treatment, avoiding surgery in 88% of pts
- ✓ Fissurectomy + BoNT needs further investigations