OARSI 2024
WORLD CONGRESS ON OSTEOARTHRITIS

VIENNA, AUSTRIA
APRIL 18–21, 2024
MESSE WIEN EXHIBITION & CONGRESS CENTER

MÉDECINE
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Inserm

Rediscovering botulinum neurotoxin A (BoNT-A) in OA

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Rééducation et Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, Cochin, AP-HP, Paris, FRANCE

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

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Christelle Nguyen, MD, PhD
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I have financial relationships with
- Advisory Board: Ipsen, Merz

AND

My presentation **does include** a discussion of off-label or investigational use

I am investigator in **5 RCTs** assessing BoNT-A for RMDs
- 2 RCTs in base-of-thumb OA (RHIBOT I, RHIBOT II)
- 1 RCT in shoulder OA (SHOTOX)
- 1 RCT in piriformis syndrom (PIRITOX)
- 1 RCT in lateral epicondylitis (EPITOX)

PHRC Recherche hospitalo- universitaires
MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

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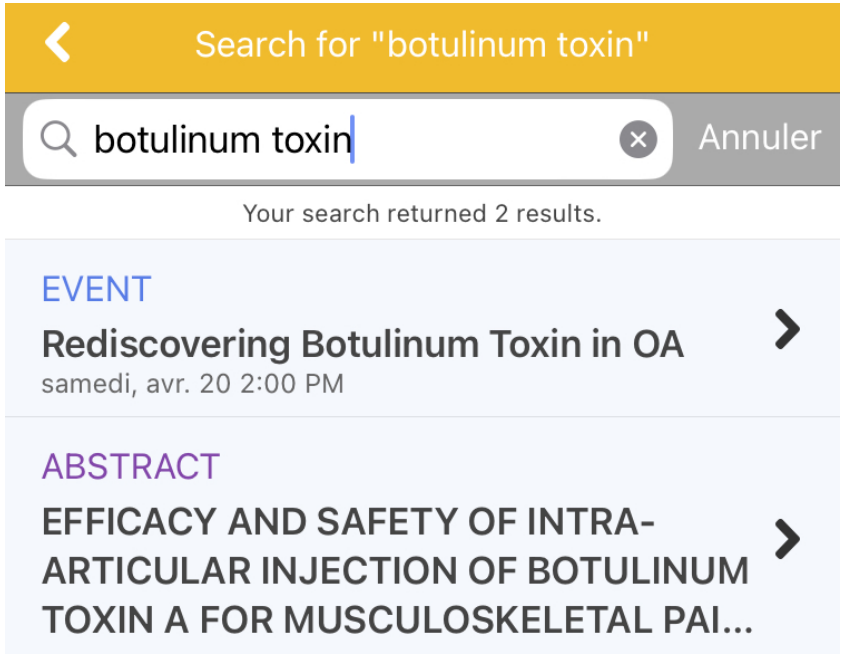


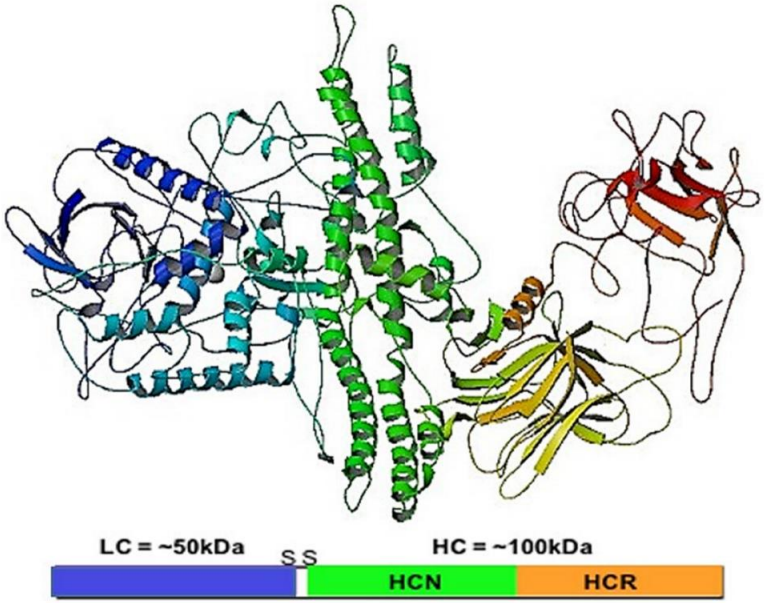
Only small interest from the OA community?

Outlines

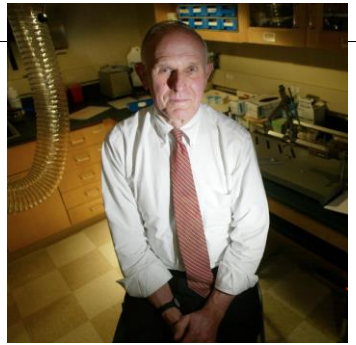
- **What rationale for BoNT-A in (RMDs and) OA?**
- What indications? What evidence?
- Safety concerns?

Botulinum toxin

- **Neurotoxin** isolated in 1944
- Produced by ***Clostridium Botulinum***
  - 1 heavy chain ➔ receptor binding
  - 1 light chain ➔ proteolytic activity
- Inhibits **acetylcholine** release at the **neuromuscular junction**
- Causes the disease **botulism**
- **7 main types** from A to G
  - A and B for medical use



Label indications



- First use **in 1978** for strabismus **(Alan B. Scott, San Franciso)**
- **Ophtalmology, neurology, aesthetic and pain medicine**
  - Oculomotricity disorders (1993)
  - Blepharospasm (1994)
  - Hemifacial spasm (1994)
  - Cervical dystonia (1994)
  - Bladder dysfunction (2000)
  - Limb spasticity (2003)
  - Severe axillary hyperhidrosis (2003)
  - Wrinkles (2003)
  - Chronic migraine (2021)

All utilisations of BoNT-A in RMDs are off-label or investigational

Approved products (France)

- **Botox®: onabotulinumtoxin A** (AbbVie)
- **Xeomin®: incobotulinumtoxin A** (Merz)
- **Dysport®: abobotulinumtoxin A** (Ipsen)

- Dose equivalent units

Table 1. Botulinum toxin products and protein content/100 units [5,6].

Nonproprietary Name	150-kD Protein Content (ng)	Total Protein (150 kD and NAP) Content (ng)	Dose Equivalent Units
Onabotulinumtoxin A	0.73	5.00	1
Incobotulinumtoxin A	0.44	0.44	1
Abobotulinumtoxin A	0.65	0.87	2–3

NAP = nontoxic accessory proteins.

Scaglione F, Toxins 2016

A Swiss army knife molecule

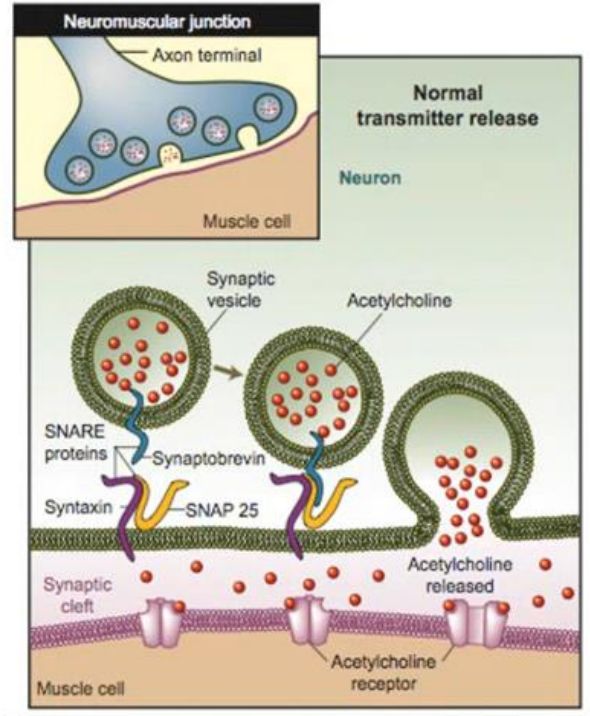
Effects are
- Delayed ~ **1 week**
- Maximal ~ **6 weeks**
- Transient ~ **3-6 months**

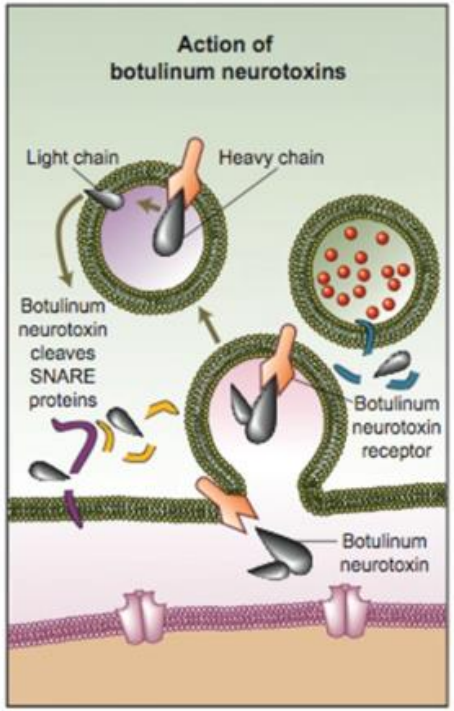
Analgesic effects
Nociceptive neurons
(Posterior horn of the spinal cord)

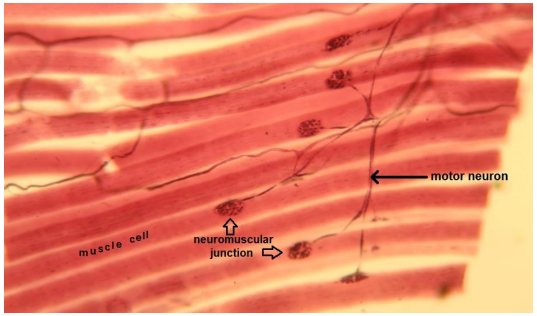
Paralyzing effects
Neuromuscular junctions

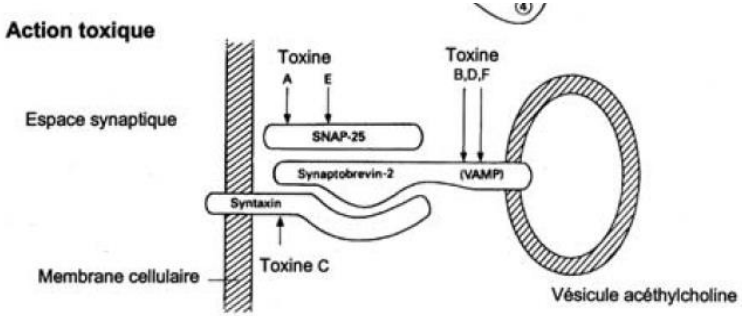
Effects on the ANS
Sympathetic and
parasympathetic neurons

Effects on neuromuscular junctions



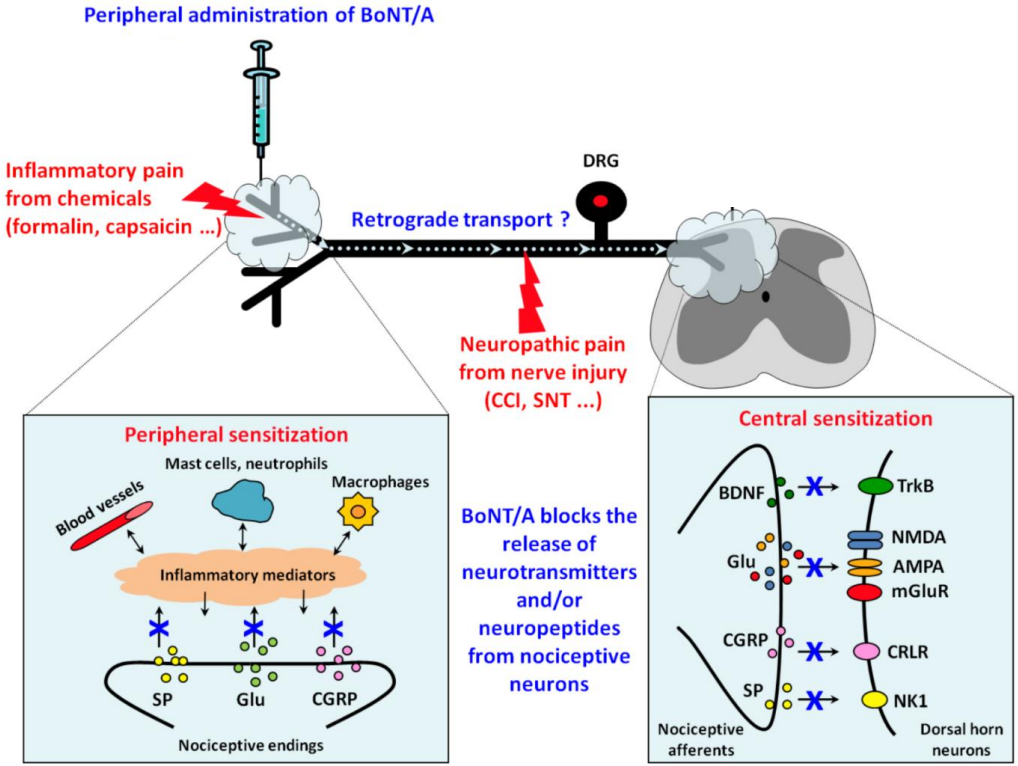






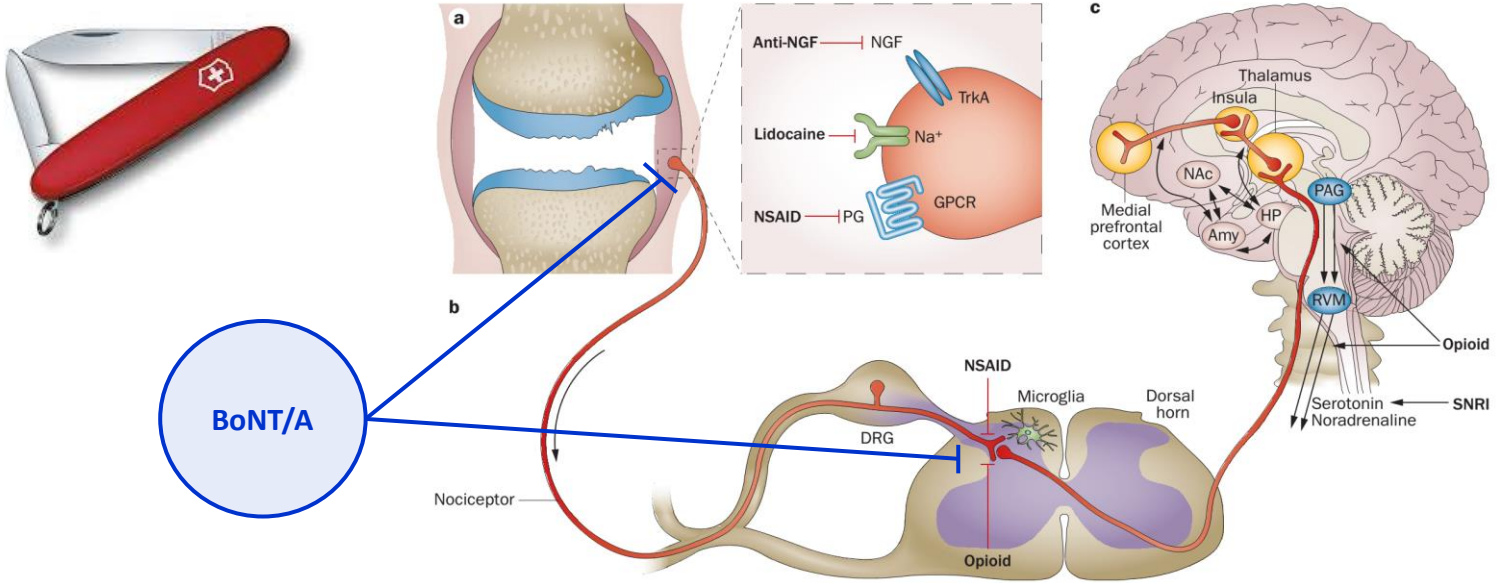
Rampel L et al. Toxins 2024

Effects on nociceptive neurons



Yoo KY et al. Neurotox Res 2014
Pavone F et Luvisetto S. Toxins 2010
Namazi H. Int Immunopharmacol 2006

BoNT-A potential positionning in OA pain?



Malfait AM, Schnitzer TJ. Nat Rev Rheumatol 2013

Outlines

- What rationale for BoNT-A in (RMDs and) OA?
- **What indications? What evidence?**
- Safety concerns?

What would be the anatomical targets in RMDs and OA?

First report of **intramuscular** BoNT-A injection for **epicondylitis** by Morré et al. in 1997

Morré HHE et al. Lancet 1997

Paralyzing effects
NMJ

Analgesic effects
Nociceptive neurons

INTRAMUSCULAR INJECTION

↘ Traction on the components of the enthesis

INTRA-ARTICULAR INJECTION

↘ Peripheral and central sensitization

Treatment of chronic tennis elbow with botulinum toxin

H H E Morré, S B Keizer, J J v Os

Uncontrolled open study, N=14
- 43 yo, 9 women
- Pain duration ~ 2.4 years
- **IM BoNT-A 30 UI**
- Outcome: **Δ pain at 6-8 months**

In an open study we have treated 14 patients (five men, nine women) with chronic treatment-resistant tennis elbow. Age varied from 34 to 60 years (mean 43 years) and the duration of symptoms from 0·6 to 6 years (mean 2·4 years). These patients were treated with 20–40 units botulinum toxin (average 30 units) injected under electromyographic guidance into the extensor digitorum communis III and IV muscle. The objective was to cause extension paresis of the third and fourth fingers which occurred in ten patients within 2 weeks after injection and in four patients after a second injection 1 month later. The paresis lasted 3–4 months and the second and fifth fingers remained unaffected. During the follow-up (6–8 months), pain relief of more than 50% on a self-assessment scale occurred in nine patients and pain disappeared completely in four patients. Pain relief occurred in ten patients within 2 weeks, in one patient within 3 weeks, and in two patients after 1 month. In one patient the pain seemed to be based on a carpal tunnel syndrome. No side-effects or complications occurred to any patient during treatment.

Morré HHE et al. Lancet 1997

Treatment of Lateral Epicondylitis with Botulinum Toxin

A Randomized, Double-Blind, Placebo-Controlled Trial

Shiu Man Wong, MB BCh; Andrew C.F. Hui, MBBS; Po-Yee Tong, BSc; Dawn W.F. Poon, BSc; Evelyn Yu, BSc; and Lawrence K.S. Wong, MD

RCT, N=60

- 45 yo, 49 women
- Pain duration ~ 8 months
- Pain intensity ~ 6.5/10
- Exp group: **IM aboBoNT-A 60 UI**
- Ctrl group: **IM saline**
- Primary outcome: **Δ pain NRS (0-100) at weeks 4 and 12**

Evaluation	Mean (SD)	
	Botulinum Toxin Group (n = 30)	Placebo Group (n = 30)
Pain intensity, *mm**		
Baseline	65.5 (15.0)	66.2 (13.2)
Week 4	25.3 (18.8)	50.5 (21.7)
Week 12	23.5 (22.3) ↘ **40 pts**	43.5 (23.9) ↘ **15 pts**
Grip strength, *kg*		
Right side		
Baseline	20.29 (5.27)	23.81 (7.28)
Week 4	17.47 (4.47)	23.13 (7.39)
Week 12	20.65 (4.89)	24.75 (7.35)
Left side		
Baseline	19.56 (5.46)	20.06 (6.60)
Week 4	18.75 (7.99)	21.41 (6.36)
Week 12	21.31 (6.96)	22.12 (6.02)

Wong SM et al. Ann Int Med 2005

Treatment of Lateral Epicondylitis with Botulinum Toxin

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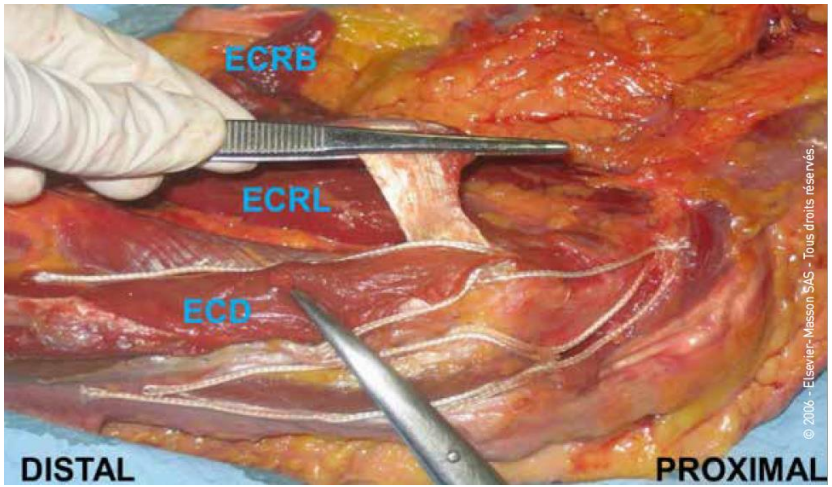
Adverse Event	Botulinum Toxin Group (n = 30), n	Placebo Group (n = 30), n	Total (n = 60), n
Postinjection			
Pain	2	1	3
Nausea	0	1	1
Week 4			
Weakness in finger extension	10	6	16
Paresis of digits	4	0	4
Week 12			
Weakness in finger extension	2	1	3
Paresis of digits	1	0	1
Total	19 63%	9	28

Wong SM et al. Ann Int Med 2005

Injecting the right muscle to reduce off-target effects

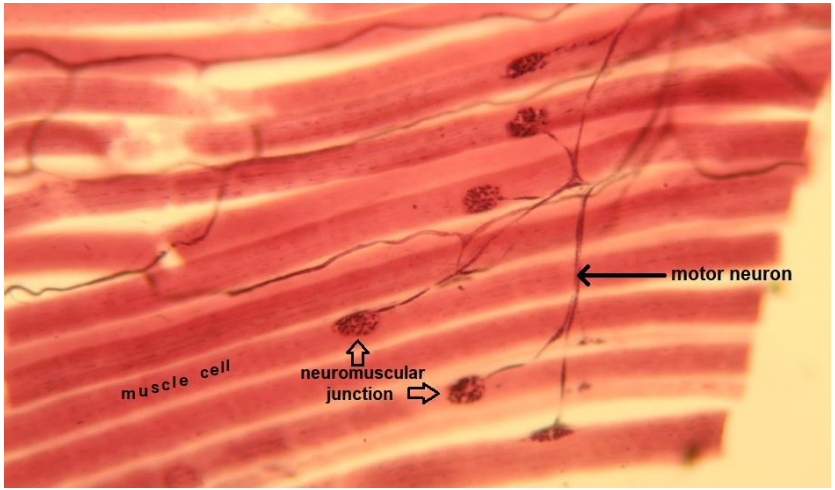


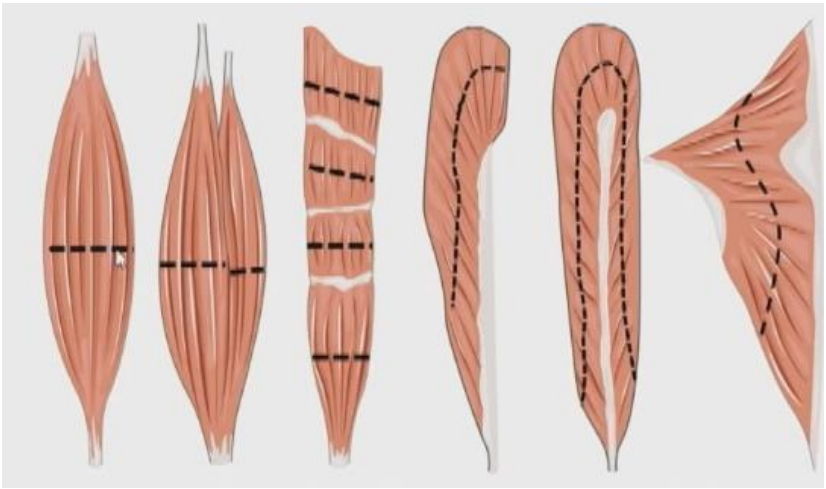
Extensor carpi radialis brevis (ECRB) = main muscle that pulls the common tendon of epicondylar muscles

↘ **frequency of paresis** of the 3rd-4th fingers ~17% (*vs* 63% in Wong's study)

Wong SM et al. Ann Int Med 2005
Creuzé A et al. J Bone Joint Surg Am 2018

Injecting the neuromuscular junction





Diffusion of BoNT-A is limited ➔ parallel to muscle fiber

Optimization of the injection techniques to efficiently access motor endplate zones

- US or EMG guidance
- At different depths perpendicular to the direction of the muscle fiber
- At higher volume

Elwischger K et al. J. Neurol Sci 2014

Intra-articular injections: 14 RCTs since 2009

Age		63
Pain intensity (/100)		60
Joints assessed	- **Knee** - Base-of-thumb - Shoulder - Ankle	**10 (N=814)** 1 (N=60) 2 (N=68) 1 (N=75)
Conditions	- **OA** - Painful TKR - OA/RA - Frozen shoulder	**11 (N=900)** 1 (N=58) 1 (N=40) 1 (N=28)
Comparators	- IA saline - IA corticosteroids - IA hyaluronan - Non-IA comparator (PT, education)	7 (N=611) 4 (N=223) 3 (N=255) 2 (N=93)
JADAD score	- ≥ 4/5	10

Gagnière M et al. Ann Phys Rehab Med 2024 (in revision)

Many « positive » meta-analyses

JB&JS OPEN ACCESS

Efficacy and Safety of Intra-Articular Botulinum Toxin A Injection for Knee Osteoarthritis

A Systematic Review, Meta-Analysis, and Meta-Regression of Clinical Trials

Yoyos Dias Ismiarto, MD, PhD, and Gregorius Thomas Prasetiyo, MD

Special Issue: Potential Diagnosis or Treatment Targets of Osteoarthritis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research 48(4) 1–10

DOI: 10.1177/0300060519895868
journals.sagepub.com/home/imr
SAGE

The efficacy and safety of Botulinum Toxin Type A in painful knee osteoarthritis: a systematic review and meta-analysis

Shuchao Zhai[1,*], Botao Huang[2,*] and Kai Yu[1]

Toxicon 241 (2024) 107656

Contents lists available at ScienceDirect

Toxicon

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

Intraarticular botulinum toxin type A versus corticosteroid or hyaluronic acid for painful knee osteoarthritis: A meta-analysis of head-to-head randomized controlled trials

Yinan Yang *, Guozheng Li, Yuping Su

Toxicon 224 (2023) 107026

Contents lists available at ScienceDirect

Toxicon

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

The efficacy and safety of intra-articular botulinum toxin type A injection for knee osteoarthritis: A meta-analysis of randomized controlled trials

Chen Wang [a,1], Jinpeng Zhao [b,1], Fang Gao [a], Min Jia [c], Luoman Hu [a], Chengfei Gao [a,*]

Some concerns

- Different locations lumped together
- Non-IA comparators lumped with IA comparators
- Omission of arms

Clinical Rehabilitation
2017, Vol. 31(4) 435–443

DOI: 10.1177/0269215516644951
journals.sagepub.com/home/cre
SAGE

Intra-articular injections of botulinum toxin a for refractory joint pain: a systematic review and meta-analysis

Tao Wu[1*], Hai-xin Song[1*], Yan Dong[2], Ye Ye[1] and Jian-hua Li[1]

Efficacy of Intra-Articular Botulinum Toxin in Osteoarticular Joint Pain

A Meta-Analysis of Randomized Controlled Trials

Courseau, Mathilde MD*; Salle, Pascale Vergne PhD*; Ranoux, Danièle MD†; de Pouilly Lachatre, Anais*

Author Information

The Clinical Journal of Pain 34(4):p 383-389, April 2018. | *DOI:* 10.1097/AJP.0000000000000538

Gagnière M et al. Ann Phys Rehab Med 2024 (in revision)

Knee OA: only one very high-quality RCT

Osteoarthritis and Cartilage

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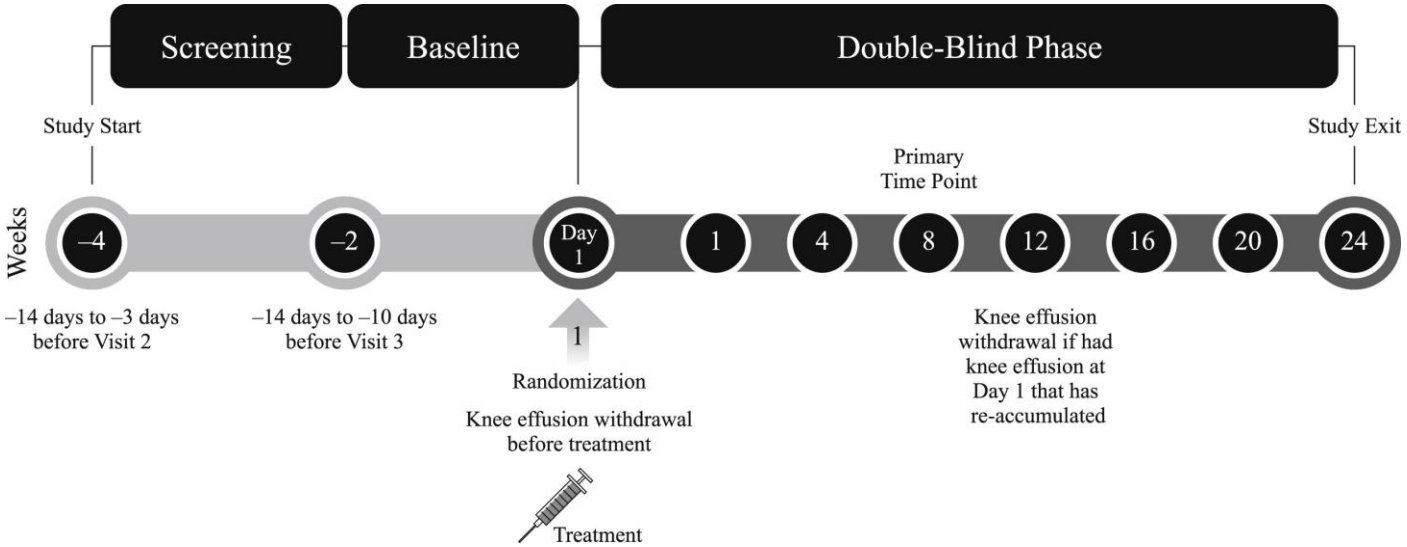
Efficacy and safety of single-dose onabotulinumtoxinA in the treatment of symptoms of osteoarthritis of the knee: results of a placebo-controlled, double-blind study

T.E. McAlindon †, U. Schmidt ‡, D. Bugarin §, S. Abrams §, T. Geib §, R.E. DeGryse §, K. Kim §, T.J. Schnitzer ‖ *

† *Division of Rheumatology, Tufts Medical Center, Boston, MA, USA*
‡ *CCBR Ballerup, Bioclinica Research Network, Denmark*
§ *Allergan Plc, Irvine, CA, USA*
‖ *Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

McAlindon T et al. Osteoarthritis Cartilage 2018

Knee OA: only one very high-quality RCT

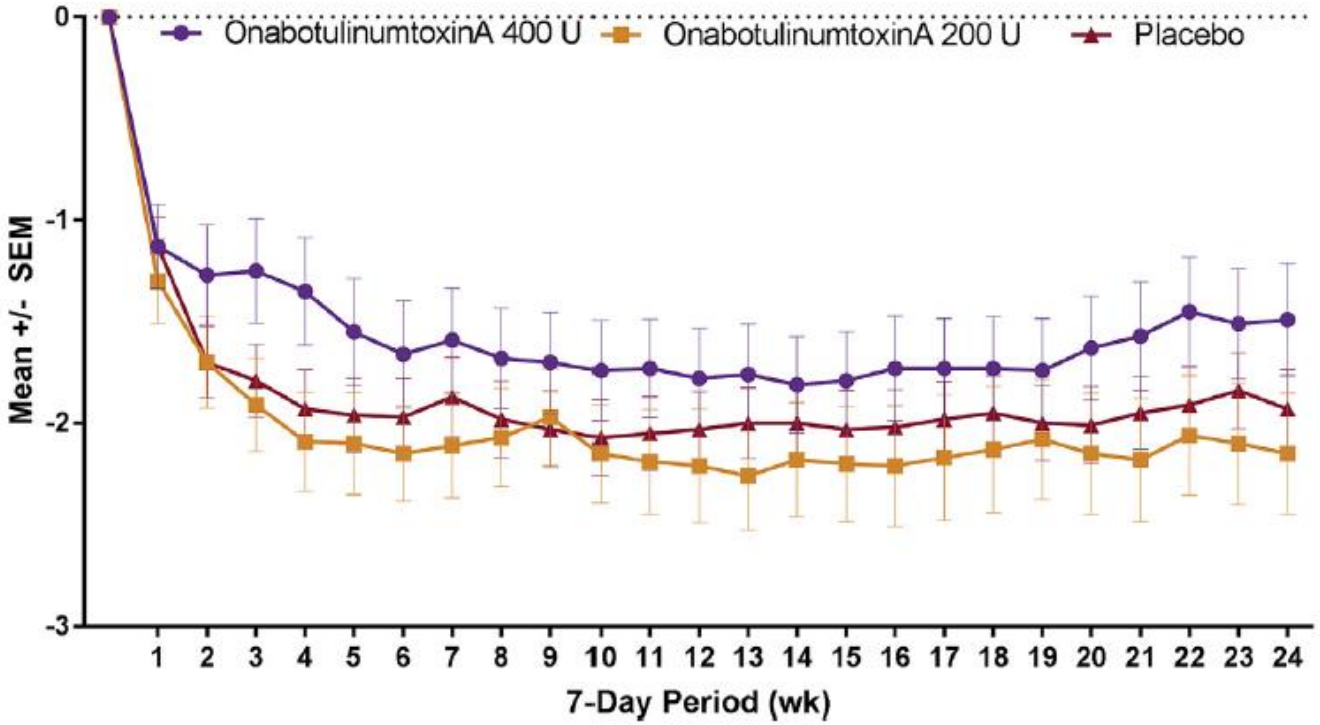


- **Experimental group 1: IA onaBoNT-A 400 UI (n=39)**
- **Experimental group 2: IA onaBoNT-A 200 UI (n=37)**
- **Control group: IA saline (n=82)**

McAlindon T et al. Osteoarthritis Cartilage 2018

Knee OA: only one very high-quality RCT

RCT, N=176
- 61 yo, 107 women
- Knee OA, KL II/III
- Pain duration ~ 9 years
- Pain intensity ~ 6/10
- Primary outcome: **pain NRS at 8 weeks**

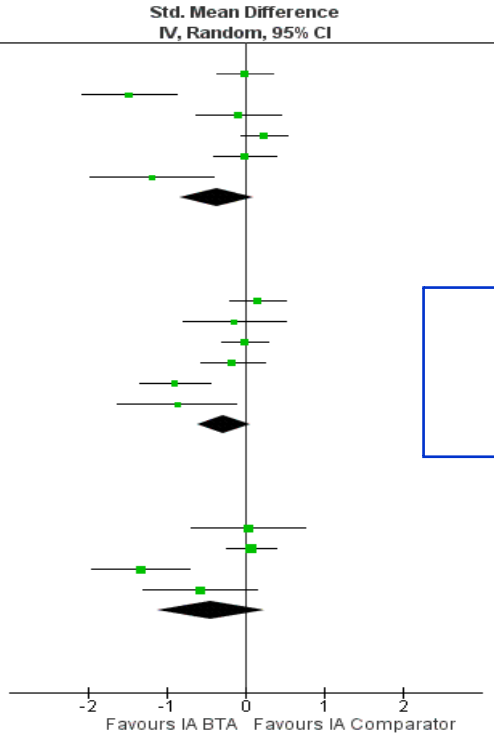


McAlindon T et al. Osteoarthritis Cartilage 2018

Quantitative synthesis for knee OA (only IA comparators)

KNEE PAIN

Study or Subgroup	IA BTA Mean	IA BTA SD	IA BTA Total	IA Comparator Mean	IA Comparator SD	IA Comparator Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.1.1 Short-term								
Arendt-Nielsen 2017	4.2	1.1	61	4.2	1.3	60	18.4%	0.00 [-0.36, 0.36]
Bao 2018	3.9	0.8	20	5.3	1	40	15.4%	-1.47 [-2.07, -0.87]
Boon 2010	5.2	2.4	40	5.4	2.3	20	16.2%	-0.08 [-0.62, 0.45]
McAlindon 2018	4.2	1.3	86	3.9	1.2	87	19.0%	0.24 [-0.06, 0.54]
Mendes 2019	1.7	2.5	35	1.7	2.5	70	17.8%	0.00 [-0.41, 0.41]
Shukla 2018	4.1	1.4	15	5.8	1.4	15	13.1%	-1.18 [-1.97, -0.40]
Subtotal (95% CI)			**257**			**292**	**100.0%**	**-0.35 [-0.82, 0.12]**
Heterogeneity: Tau² = 0.28; Chi² = 32.70, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 1.45 (P = 0.15)								
5.1.2 Intermediate-term								
Arendt-Nielsen 2017	4.2	1.1	61	4	1.3	60	19.4%	0.17 [-0.19, 0.52]
Boon 2010	4.9	2.2	28	5.2	2.1	13	12.9%	-0.14 [-0.79, 0.52]
McAlindon 2018	40	1.3	86	40	1.2	87	20.7%	0.00 [-0.30, 0.30]
Mendes 2019	1.3	2.2	35	1.7	2.6	70	18.3%	-0.16 [-0.57, 0.25]
Rezasoltani 2020	7.4	6.5	28	13.3	6.6	82	17.4%	-0.89 [-1.34, -0.45]
Shukla 2018	4.6	1.7	15	5.9	1.2	15	11.3%	-0.86 [-1.61, -0.11]
Subtotal (95% CI)			**253**			**327**	**100.0%**	**-0.27 [-0.61, 0.08]**
Heterogeneity: Tau² = 0.13; Chi² = 17.94, df = 5 (P = 0.003); I² = 72%								
Test for overall effect: Z = 1.52 (P = 0.13)								
5.1.3 Long-term								
Boon 2010	5.2	2.3	21	5.1	2.8	11	23.0%	0.04 [-0.69, 0.77]
McAlindon 2018	4.2	1.3	76	4.1	1.2	82	29.2%	0.08 [-0.23, 0.39]
Rezasoltani 2021	2.8	1.6	25	5.1	1.8	25	24.8%	-1.33 [-1.95, -0.71]
Shukla 2018	5.2	1.5	15	6	1.2	15	23.0%	-0.57 [-1.31, 0.16]
Subtotal (95% CI)			**137**			**133**	**100.0%**	**-0.43 [-1.12, 0.26]**
Heterogeneity: Tau² = 0.39; Chi² = 17.33, df = 3 (P = 0.0006); I² = 83%								
Test for overall effect: Z = 1.23 (P = 0.22)								



100-400 UI
RCT=6
N=549

Gagnière M et al. Poster 849, OARSI 2024

Shall we throw out BoNT-A for RMDs with the bath water?

Changes in intra-articular biomarkers

Percentage change in biomarker concentration at week 12 after IA onabotulinumtoxinA or placebo

Biomarker*	OnabotulinumtoxinA 400 U ($n = 5$)†	OnabotulinumtoxinA 200 U ($n = 4$)†	Placebo ($n = 9$)†
Glutamine	0.6 (4.6) [$n = 3$]	−9.0 (7.5) [$n = 3$]‡	31.7 (54.6) [$n = 4$]
Substance P	−17.1 (26.1) [$n = 2$]	−12.7 (34.1) [$n = 2$]	1.3 (35.8) [$n = 4$]
CTX-2	−75.4 [$n = 1$]§	−16.0 [$n = 1$]§	90.8 (196.9) [$n = 4$]
CTX-1	17.6 [$n = 1$]§	−9.1 (9.0) [$n = 2$]	−10.9 (15.3) [$n = 5$]
Aggrecan	−14.8 (25.5) [$n = 5$]	−7.3 (14.2) [$n = 4$]	19.4 (47.8) [$n = 9$]
MMP-1	7.2 (22.9) [$n = 4$]	−1.4 (38.6) [$n = 4$]	29.0 (125.6) [$n = 9$]
MMP-3	−10.6 (22.1) [$n = 5$]	−4.2 (15.8) [$n = 4$]	12.3 (52.9) [$n = 9$]
MMP-9	−2.1 (56.2) [$n = 3$]	20.6 (52.0) [$n = 2$]	−1.4 (7.6) [$n = 2$]
Hyaluronic acid	−0.1 (31.5) [$n = 5$]	1.8 (10.1) [$n = 4$]	3.6 (21.7) [$n = 9$]
IL-6	168.0 (305) [$n = 5$]	52.6 (95.6) [$n = 4$]	117.0 (347) [$n = 9$]

McAlindon T et al. Osteoarthritis Cartilage 2018

↘ in pain sensitization in a « nociceptive » subpopulation

RCT, N=121
- 62 yo, 62 women
- Knee OA, KL I/II/III
- Pain duration ~ 9 years
- Exp group: IA OnaBoNT-A 200 UI
- Ctrl group: IA saline
- Primary outcome: **pain biomarkers**
- **« Nociceptive » subpopulation: PainDetect-Questionnaire ≤ 12**

Outcome	OnabotulinumtoxinA n = 36	Placebo n = 32	Total n = 68	p value
Mean (se) QST by knee PPT*				
Baseline, kPa	265.4 (24.9)	286.2 (24.8)	275.2 (17.5)	0.370
Week 4 change from baseline, %	28.3 (7.8)	17.4 (10.5)	23.1 (6.5)	0.107
Week 8 change from baseline, %	29.5 (7.5)	34.8 (15.8)	32.0 (8.4)	0.278
Week 12 change from baseline, %	28.5 (8.6)	31.1 (15.6)	29.7 (8.6)	0.620
Mean (se) spreading sensitization by PPT†				
Tibialis anterior (leg)				
Baseline, kPa	197.1 (17.1)	234.3 (16.8)	214.6 (12.1)	0.129
Week 4 change from baseline, %	33.3 (9.9)	4.9 (6.1)	19.8 (6.2)	**0.030**
Week 8 change from baseline, %	35.5 (8.5)	6.6 (6.4)	22.0 (5.7)	**0.021**
Week 12 change from baseline, %	26.8 (7.2)	13.1 (8.4)	20.3 (5.5)	0.134
Extensor carpi radialis longus (arm)				
Baseline, kPa	290.1 (19.8)	317.6 (21.2)	303.1 (14.5)	0.314
Week 4 change from baseline, %	22.0 (5.8)	16.3 (12.0)	19.3 (6.4)	**0.027**
Week 8 change from baseline, %	24.4 (6.3)	23.9 (13.9)	24.2 (7.3)	0.230
Week 12 change from baseline, %	31.0 (9.8)	20.9 (13.3)	26.2 (8.1)	0.267
Mean (se) spreading sensitization by total area of knee pain‡				
Study knee				
Baseline, cm^2	1.1 (0.2)	1.3 (0.2)	1.2 (0.1)	0.226
Week 4 change from baseline, %	18.3 (42.2)	5.8 (15.3)	12.4 (23.1)	0.276
Week 8 change from baseline, %	1.7 (34.4)	−5.0 (16.5)	−1.4 (19.7)	0.345
Week 12 change from baseline, %	88.2 (98.1)	−18.3 (16.9)	37.3 (51.9)	0.835
Contralateral knee				
Baseline, cm^2	0.8 (0.2)	0.2 (0.1)	0.5 (0.1)	**0.001**
Week 4 change from baseline, %	−27.7 (12.5)	29.9 (38.1)	−13.8 (13.7)	0.145
Week 8 change from baseline, %	−43.7 (13.1)	6.3 (30.2)	−31.2 (12.8)	0.109
Week 12 change from baseline, %	−45.0 (15.4)	28.7 (45.8)	−26.6 (16.9)	0.125

Arendt-Nielsen L et al. Scand J Rheumatol 2017

What about smaller, non-weight-bearing, upper limb joints?

RHIZORTHESE TRIAL

Splinting: ↘ **pain,** ↗ **function at 12 months**
➔ **Gap between baseline and 12 months**

- IA GC and hyaluronan not recommended
- Safety profile concerns with other medication
- **Candidate molecule: IA BoNT-A?**
  - Prolonged effects ~ 3-6 months
  - Analgesic + paralyzing effect (joint rest)

Rannou F et al. Ann Int Med 2009

RHIBOT TRIAL

+

RCT, N=60

- 65 yo, 47 women, base-of-thumb OA
- Pain duration ~ 6.5 years
- Pain intensity ~ 6/10
- Experimental group: **IA onaBoNT-A 50 UI + splint**
- Control group: **IA saline + splint**
- Primary outcome: **Δ pain NRS (0-100) at 3 months**

Gil C et al. BMJ Open 2018

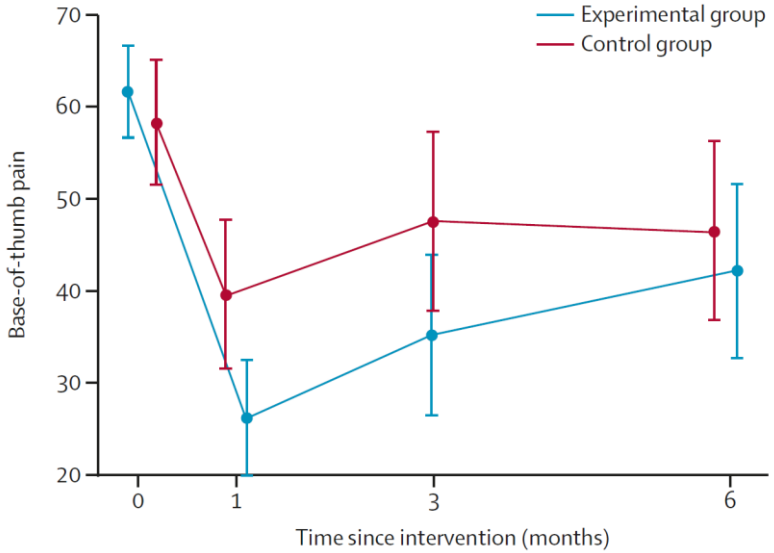
Intra-articular botulinum toxin A injection for painful base-of-thumb osteoarthritis: a double-blind, randomised, controlled, phase 3 trial (RHIBOT)

Christelle Nguyen, Hendy Abdoul, Raphaël Campagna, Henri Guerini*, Léa Jilet, Catherine Bedin, Franck Chagny, Gaëlle Couraud, Camille Daste, Jean-Luc Drapé, Rémy Fléchon, Charlotte Gil, Corinne Guérin, Marie-Martine Lefèvre-Colau, Serge Poiraudeau†, Estelle Randriamampandry, Alexandra Roren, Antoine Feydy, François Rannou*

Nguyen C et al. Lancet Rheumatol 2022

Results

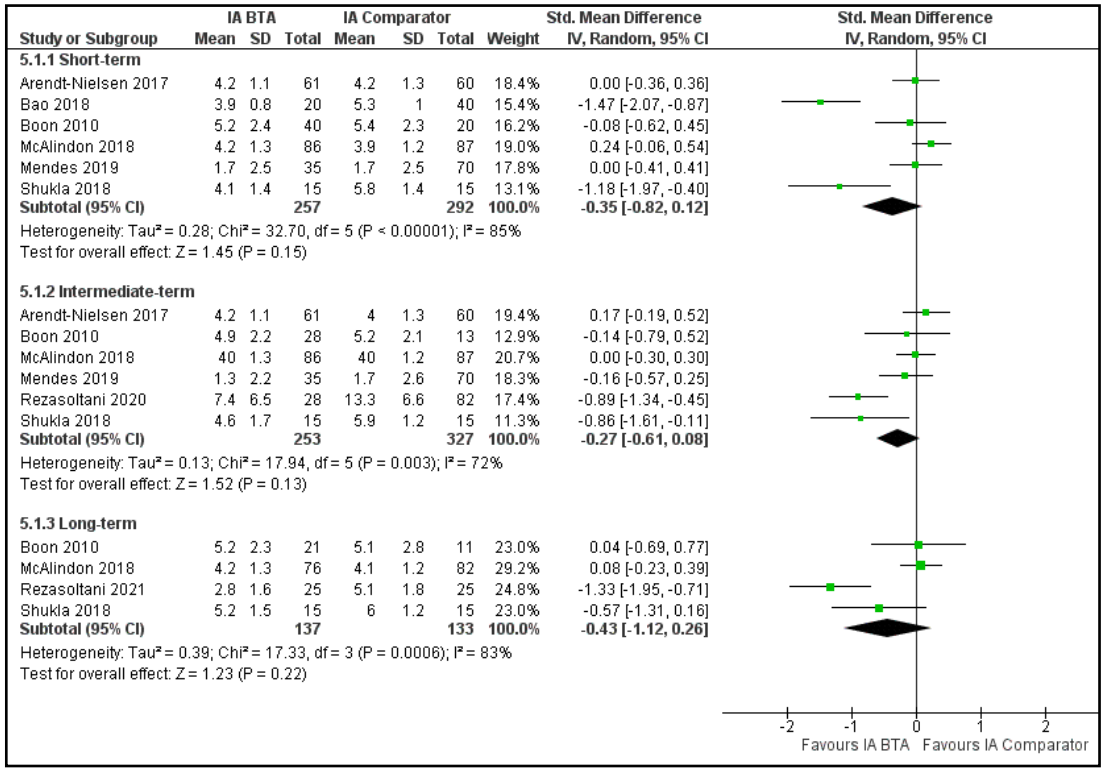
	OnaBoNT-A + Orthosis (n=30)	Saline + Orthosis (n=30)	Absolute difference (95% CI)	P
• Δ pain NRS (0-100) at 1 month	-34.3 (-42.9 to -25.7)	-18.0 (-26.2 to -9.8)	-16.3 (-27.9 to -4.7)	0.004
• **Δ pain NRS (0-100) at 3 months**	**-25.7 (-35.5 to -15.8)**	**-9.7 (-17.1 to -2.2)**	**-16.0 (-28.1 to -3.9)**	**0.043**
• Δ pain NRS (0-100) at 6 months	-18.3 (-26.9 to -9.8)	-11.7 (-21.2 to -2.2)	-6.7 (-19.2 to 5.9)	0.367
• OARSI responders at 3 months	**22 (73)**	**18 (60)**	13.3 (-10.3 à 37.0)	0.273



Effect-size: **0.7** (0.2-1.2)

Nguyen C et al. Lancet Rheumatol 2022

Inconsistent results with knee OA trials

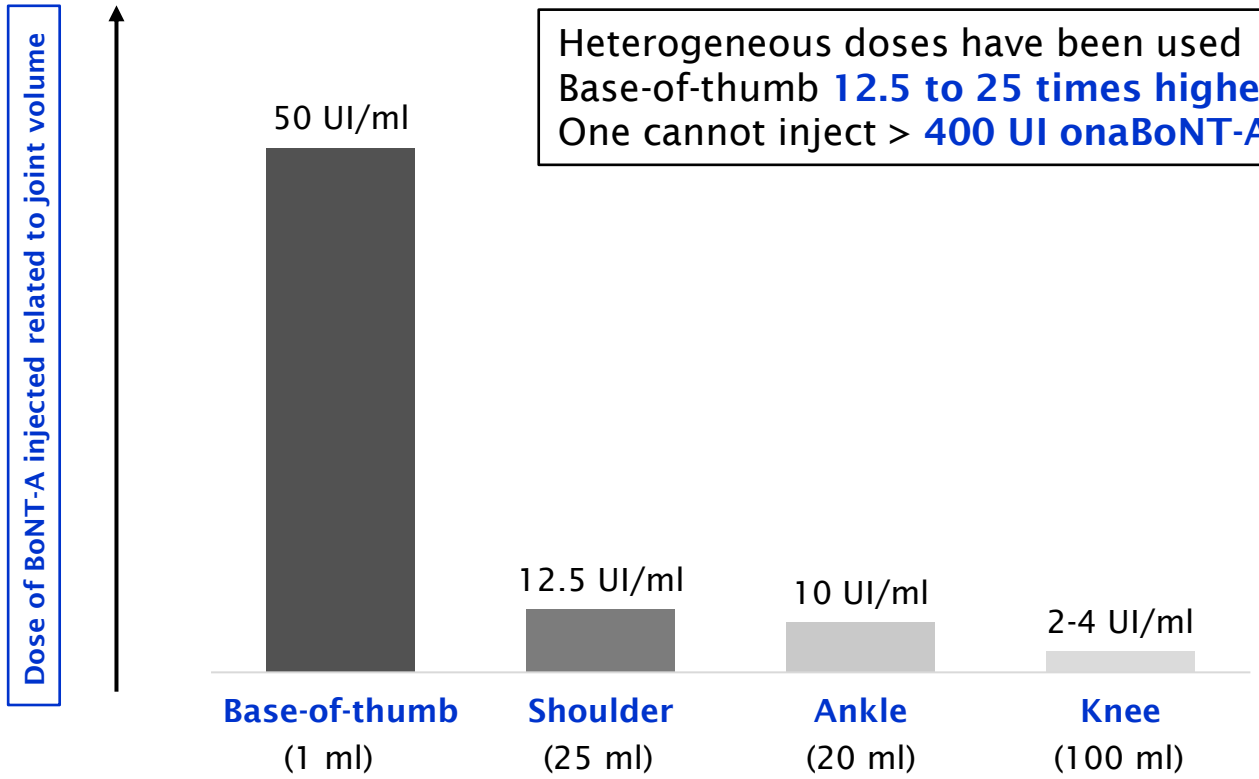


4 key differences with knee OA trials

- Participants in a « more » chronic phase of OA: ↗ sensitization?
- Add-on therapy to the rest orthosis
- **Synergistic effects with muscle motor deficit:** -30.8 (N=14) vs -22.2 (N=16) points at 3 months, in participants with and without deficit, respectively
- **Smaller joint ➔ higher dose injected related to the joint volume**

Gagnière M et al. Poster 849, OARSI 2024

Efficacy may depend on BoNT-A dose related to joint volume



Heterogeneous doses have been used
Base-of-thumb **12.5 to 25 times higher** than knee
One cannot inject > **400 UI onaBoNT-A per visit (FDA)**

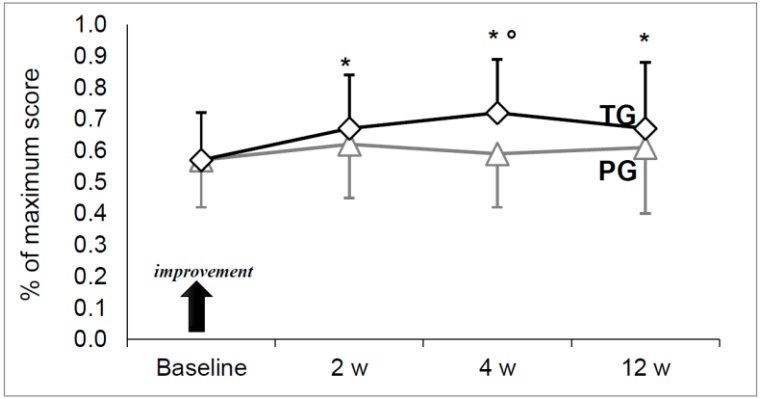
Gagnière M et al. Poster 849, OARSI 2024

Intramuscular instead of intra-articular injection?

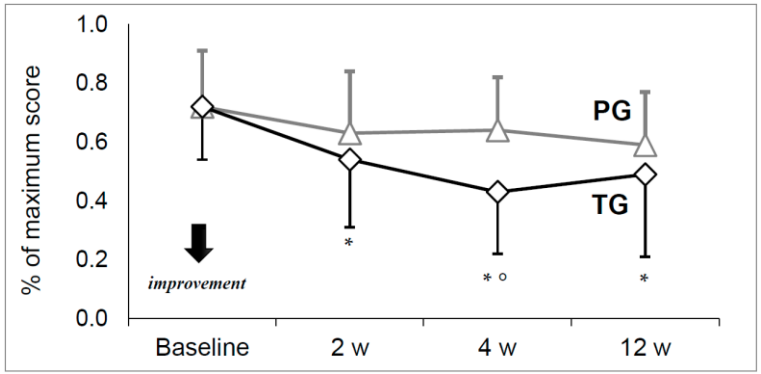
RCT, N=46
Hypothesis: ↗ activation of adductor muscles in hip OA

- 62 yo, 25 women, hip OA, KL II/III
- Pain intensity ~ 7/10
- TG: **IM aboBoNT-A 400 UI**
- PG: **IM saline**
- Primary outcomes: **HHS and pain VAS at 4 weeks**

Harris Hip Score



Pain VAS



Eleopra R et al. Toxins 2018

Outlines

- What rationale for BoNT-A in (RMDs and) OA?
- What indications? What evidence?
- **Safety concerns?**

Safety concerns?

	OnaBoNT-A + Orthosis (n=30)	Saline + Orthosis (n=30)
Serious adverse events	**0**	**0**
Minor adverse events	**48**	**40**
• Hand pain	6 (20)	11 (37)
• **Tenar muscle motor deficit**	**14 (47)**	**2 (7)**
• Musculoskeletal pain	5 (17)	6 (20)
• Infection	1 (3)	2 (7)
• Hand paresthesia	1 (3)	1 (3)
• Local bleeding	0 (0)	1 (3)
• Thrombophlebitis	0 (0)	1 (3)

Nguyen C et al. Lancet Rheumatol 2022

In the 14 RCTs of intra-articular BoNT-A

- No studies reported any serious adverse events
- The frequency of minor adverse events was similar in both groups

Gagnière M et al. Poster 849, OARSI 2024

Rapidly progressive OA?

12 weeks after intra-articular injection

Variable	IA BoNT/A n = 6	IA Placebo n = 6	P-value
Cartilage structure	3 (0–3)	4 (2–7)	0.534
Synovial structure	3 (3–4)	3 (2–4)	0.593
Synovial infiltrates	1 (1–2)	2 (1–2)	0.638

Changes are presented as median and IQR.
IA BoNT/A, intra-articular botulinum toxin A; placebo, 0.9% saline.

Heikkilä HM et al. PLoS One 2018

First study on cartilage explants
BoNT-A (0, 1, 10, 50, 100, 500 pg/mL) for 96 hrs
No effects on cartilage homeostasis: inflammation (PGE2), ECM degradation (sGAGs CS846), cell apoptosis (TUNEL)

McCarthy MB et al. Am J Vet Res 2023

Take home messages

Repositioning “old” molecules like BoNT-A as IA targeted biologics for OA pain

- Strong rationale for OA pain ➔ effects on peripheral and central sensitization
- Evidence from small RCTs ➔ epicondylitis and base-of-thumb OA
- No evidence in other indications ➔ dose related to joint volume ? Weight-bearing ?

In our department

- Offered off label after first-line treatments have failed
- In well-phenotyped patients (consistent anatomical target, nociceptive OA)
- Never as a stand alone treatment
- All injections under US-guidance, by experienced operator

Future directions

Going back to the bench

- Effects (and harms) of IA BoNT-A on specific preclinical models of OA
- Effects (and harms) of IA BoNT-A on joint biomechanics, cinematics
- Optimized effects with newly engineered BoNT-A or from other *Clostridium*

Getting back to colleagues with experience of BoNT-A: 5 D's of BoNT

Journal of Cosmetic and Laser Therapy. 2008; 10: 93–102

informa
healthcare

ORIGINAL ARTICLE

The five D's of botulinum toxin: Doses, dilution, diffusion, duration and dogma

ANA PAULA DE SA EARP & ELLEN S. MARMUR

The Mount Sinai Medical Center, Dermatology, New York, NY, USA

de Sa Earp AP et al. J Cosmet Laser Ther 2008

Launching of **RHIBOT II trial**: September 2024

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Thank you!

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