Université Paris Cité

Efficacy and safety of intra-articular injection of botulinum toxin A for musculoskeletal pain: a systematic review and meta-analysis

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Disclosures

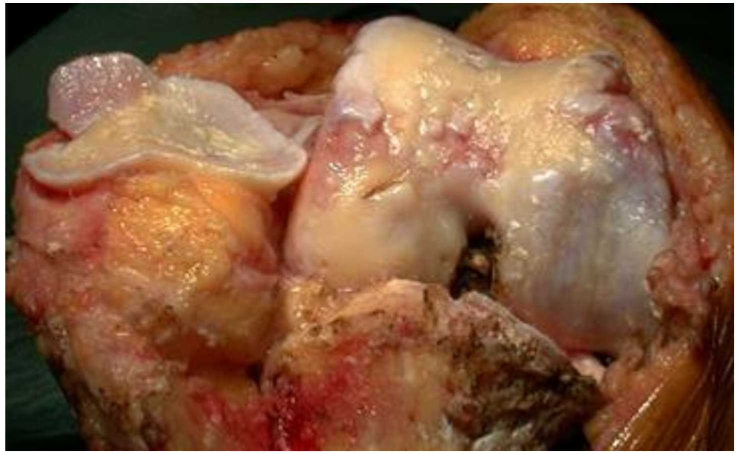
Advisory Board: Ipsen, Merz

<u>AND</u>

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

Osteoarthritis (OA)

- Most frequent rheumatic disease
- Affects all the components of the joint



365 million individuals in the world

60% females

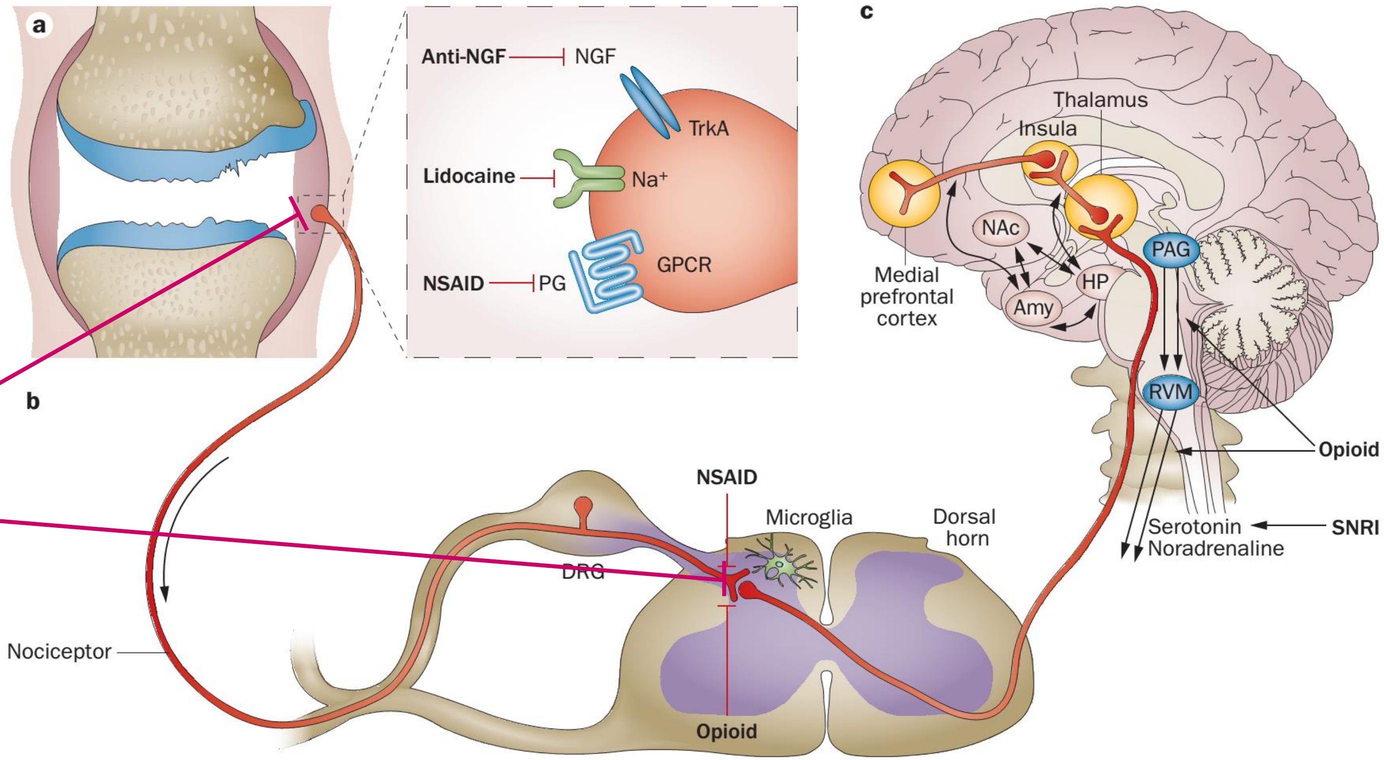
70% older than 55 years

- **Key symptoms**
  - **Joint pain**
  - Joint-specific impairments and activity limitations

WHO OA key facts 2023
Long H et al. Arthritis Rheumatol. 2022

OA pain and OA pain targets

BoNT/A



BoNT/A ➔ highly relevant candidate molecule to target OA pain

- **Targets:** nociceptive neurons and posterior horn
- **Effects:** ➘ nociception and ➘ sensitization

Malfait AM, Schnitzer TJ. Nat Rev Rheumatol, 2013

Many « positive » meta-analyses of intra-articular BoNT/A

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

Toxicon 241 (2024) 107656
Contents lists available at ScienceDirect
ELSEVIER
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

Share several drawbacks

- Diverse joint locations and conditions lumped together
- Non-intra-articular comparators lumped with intra-articular comparators
- Arms omitted from the analyses

Special Issue: Potential Diagnosis or Treatment Targets of Osteoarthritis
Journal of INTERNATIONAL MEDICAL RESEARCH
Journal of International Medical Research
48(4) 1–10
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DOI: 10.1177/0300060519895868
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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 224 (2023) 107026
Contents lists available at ScienceDirect
ELSEVIER
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,*]

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

Clinical Rehabilitation
2017, Vol. 31(4) 435–443
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DOI: 10.1177/0269215516644951
journals.sagepub.com/home/cre
SAGE

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

Primary objective

To assess the efficacy of intra-articular BoNT/A for the treatment of joint pain with more homogeneous locations, conditions and comparators

Methods

Interpretation
SMD < 0.2 → null effects
SMD 0.2 to 0.5 → weak effects
SMD 0.5 to 0.8 → moderate effects
SMD > 0.8 → large effects

- **Design.** Systematic review of RCTs with meta-analysis when possible
- **Participants.** Adults with chronic (> 3 month-duration) joint pain (any location, any condition)
- **Interventions.** Intra-articular BoNT-A (any dosage, US or landmark-guided)
- **Comparators.** Other intra-articular treatments or non-intra-articular treatments or usual care
- **Outcomes.** In the short (< 3 months), intermediate (3-6 months) and long term (> 6 months)
    - Joint pain
    - Joint-specific activity limitations
    - Adverse events
- **Search strategy.** MEDLINE, EMBASE, ClinicalTrials.gov, CINHAL and ICTRP databases were searched from inception **to July 9, 2023**. Two independent reviewers selected studies and extracted data, in a standardized manner
- **Statistical analysis.** The results of quantitative synthesis were expressed as **standardized mean difference (SMD)** (95% CI). We performed a meta-analysis when appropriate. The study was registered at www.crd.york.ac.uk/prospero (CRD4202190157)

Results

Efficacy and safety of intra-articular injection therapy of botulinum toxin for joint pain: a systematic review and meta-analysis

Mathieu Gagnière MD, Camille Daste MD, MPH, Raphaël Campagna MD, Jean-Luc Drapé MD, PhD, Antoine Feydy MD, PhD, Henri Guerini MD, Marie-Martine Lefèvre-Colau MD, PhD, François Rannou MD, PhD, Christelle Nguyen MD, PhD

Gagnière M et al, Ann Phys Rehab Med 2024 (in press)

Flow

PubMed (N=118), Embase (N=66), CT.gov (N=16), CINHAL (N=1), ICTRP (N=1)
Search conducted on November 8, 2021, updated on July 9, 2023
Records screened after duplicates removed N=188

Abstracts and titles excluded, N=166

1. Review, N=41
2. Meta-analysis, N=10
3. Case report, N=6
4. Letter, N=5
5. Observational study, N=3
6. Non randomized, N=8
7. Conditions other than joint pain, N=11
8. Interventions other than intra-articular injection of BoNT A, N=12
9. Off topic, N=30
10. Duplicate, N=8
11. Other, N=32

Full texts reviewed, N=22

Full texts excluded, N=3

1. Letter, N=1
2. Intervention reported other than intra-articular injection of BoNT A, N=1
3. Duplicate, N=1

Full texts assessed for eligibility, N=19

Studies excluded (data not available), N=5

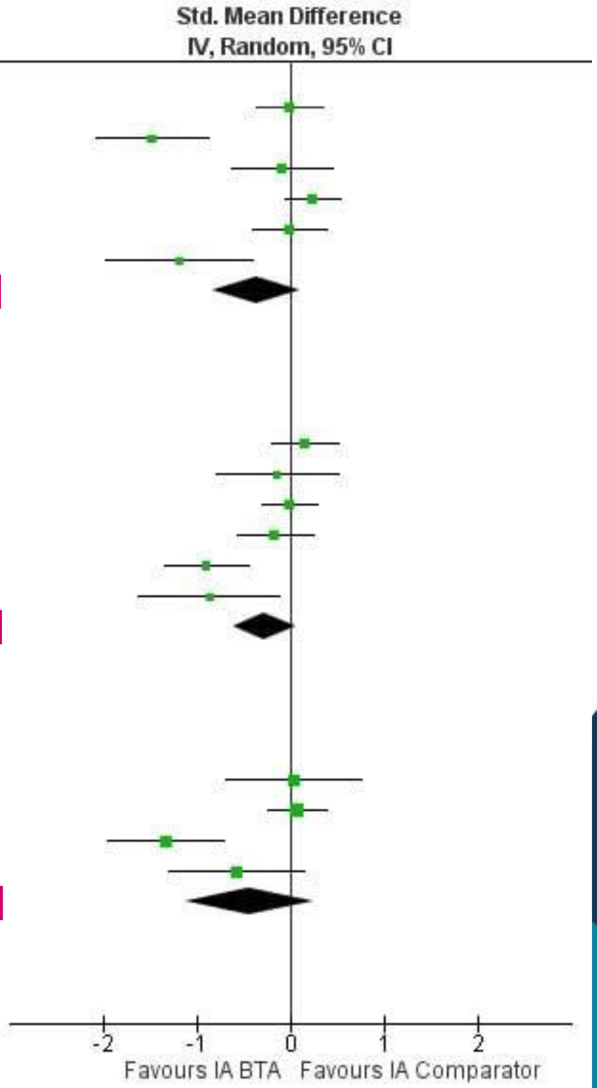
Studies included in qualitative and quantitative synthesis, N=14

14 RCTs since 2009

Age		63
Pain intensity (/100)		60
Joints assessed	**- Knee** - Ankle - Shoulder - Base-of-thumb	**10 (N=814)** 1 (N=75) 2 (N=68) 1 (N=60)
Conditions	**- OA** - Painful total knee replacement - OA and rheumatoid arthritis - Frozen shoulder	**11 (N=900)** 1 (N=58) 1 (N=40) 1 (N=28)
Comparators	**- IA saline** - IA corticosteroids - IA hyaluronan **- Non-IA comparator (physical therapy, education)**	**7 (N=611)** 4 (N=223) 3 (N=255) **2 (N=93)**
JADAD score	**- ≥ 4/5**	**10/14 (71)**

Knee: pain outcomes (vs IA comparators)

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 [32]	4.2	1.1	61	4.2	1.3	60	18.4%	0.00 [-0.36, 0.36]
Bao 2018 [27]	3.9	0.8	20	5.3	1	40	15.4%	-1.47 [-2.07, -0.87]
Boon 2010 [31]	5.2	2.4	40	5.4	2.3	20	16.2%	-0.08 [-0.62, 0.45]
McAlindon 2018 [33]	4.2	1.3	86	3.9	1.2	87	19.0%	0.24 [-0.06, 0.54]
Mendes 2019 [30]	1.7	2.5	35	1.7	2.5	70	17.8%	0.00 [-0.41, 0.41]
Shukla 2018 [26]	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 [32]	4.2	1.1	61	4	1.3	60	19.4%	0.17 [-0.19, 0.52]
Boon 2010 [31]	4.9	2.2	28	5.2	2.1	13	12.9%	-0.14 [-0.79, 0.52]
McAlindon 2018 [33]	40	1.3	86	40	1.2	87	20.7%	0.00 [-0.30, 0.30]
Mendes 2019 [30]	1.3	2.2	35	1.7	2.6	70	18.3%	-0.16 [-0.57, 0.25]
Rezasoltani 2020 [28]	7.4	6.5	28	13.3	6.6	82	17.4%	-0.89 [-1.34, -0.45]
Shukla 2018 [26]	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 [31]	5.2	2.3	21	5.1	2.8	11	23.0%	0.04 [-0.69, 0.77]
McAlindon 2018 [33]	4.2	1.3	76	4.1	1.2	82	29.2%	0.08 [-0.23, 0.39]
Rezasoltani 2021 [29]	2.8	1.6	25	5.1	1.8	25	24.8%	-1.33 [-1.95, -0.71]
Shukla 2018 [26]	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)								



N=549

N=582

N=270

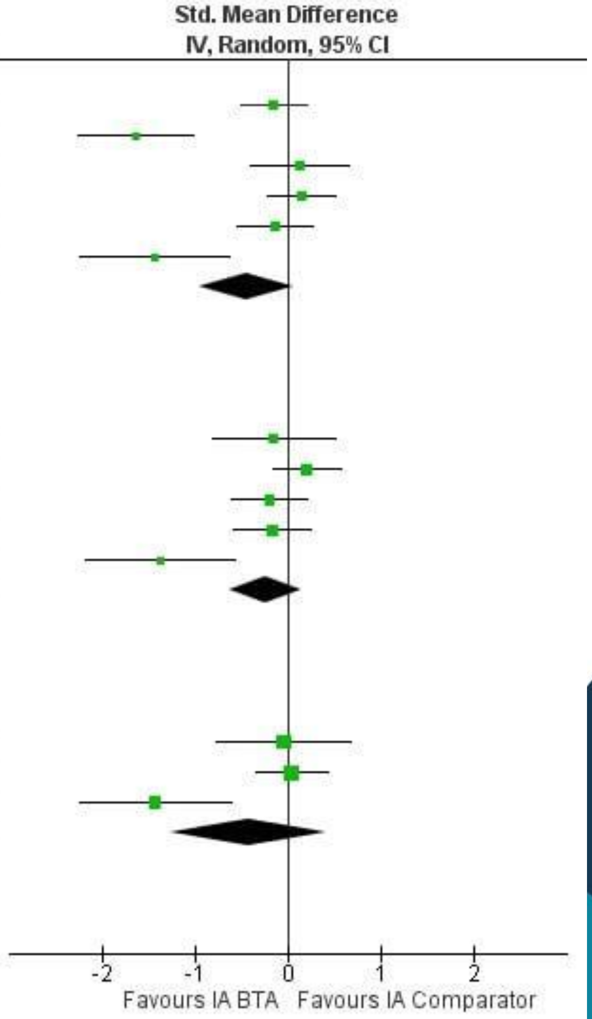
Knee: activity limitations outcomes (vs IA comparators)

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
5.2.1 Short-term								
Arendt-Nielsen 2017 [32]	39.3	36.5	61	44.7	37.4	60	18.4%	-0.15 [-0.50, 0.21]
Bao 2018 [27]	29.1	3.9	20	37.3	5.4	40	15.6%	-1.63 [-2.25, -1.02]
Boon 2010 [31]	26.7	12.1	40	25.1	10.7	20	16.5%	0.14 [-0.40, 0.67]
McAlindon 2018 [33]	4	1.9	43	3.7	1.9	87	18.3%	0.16 [-0.21, 0.52]
Mendes 2019 [30]	26.3	16.6	35	28.5	17.5	70	17.9%	-0.13 [-0.53, 0.28]
Shukla 2018 [26]	29.9	6	15	42.2	10.2	15	13.4%	-1.43 [-2.24, -0.62]
Subtotal (95% CI)			**214**			**292**	**100.0%**	**-0.44 [-0.96, 0.07]**
Heterogeneity: Tau² = 0.34; Chi² = 34.79, df = 5 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.70 (P = 0.09)								
5.2.2 Intermediate-term								
Boon 2010 [31]	24.6	10.4	28	26.1	10.2	13	16.4%	-0.14 [-0.80, 0.52]
McAlindon 2018 [33]	4	2	43	3.6	1.9	87	24.4%	0.21 [-0.16, 0.57]
Mendes 2019 [30]	25.4	15.6	35	28.9	19.9	70	23.2%	-0.19 [-0.59, 0.22]
Rezasoltani 2020 [28]	16.3	100	29	24.9	14.5	82	22.7%	-0.16 [-0.59, 0.26]
Shukla 2018 [26]	28.7	5.4	15	41.7	11.9	15	13.3%	-1.37 [-2.18, -0.56]
Subtotal (95% CI)			**150**			**267**	**100.0%**	**-0.24 [-0.63, 0.15]**
Heterogeneity: Tau² = 0.13; Chi² = 12.39, df = 4 (P = 0.01); I² = 68%								
Test for overall effect: Z = 1.19 (P = 0.23)								
5.2.3 Long-term								
Boon 2010 [31]	27.8	10.1	21	28.2	12.2	11	31.7%	-0.04 [-0.77, 0.69]
McAlindon 2018 [33]	4	1.9	39	3.9	1.9	82	38.4%	0.05 [-0.33, 0.43]
Shukla 2018 [26]	27.4	4.3	15	40.6	12	15	29.9%	-1.42 [-2.24, -0.61]
Subtotal (95% CI)			**75**			**108**	**100.0%**	**-0.42 [-1.26, 0.42]**
Heterogeneity: Tau² = 0.44; Chi² = 10.57, df = 2 (P = 0.005); I² = 81%								
Test for overall effect: Z = 0.98 (P = 0.33)								

N=506

N=417

N=183



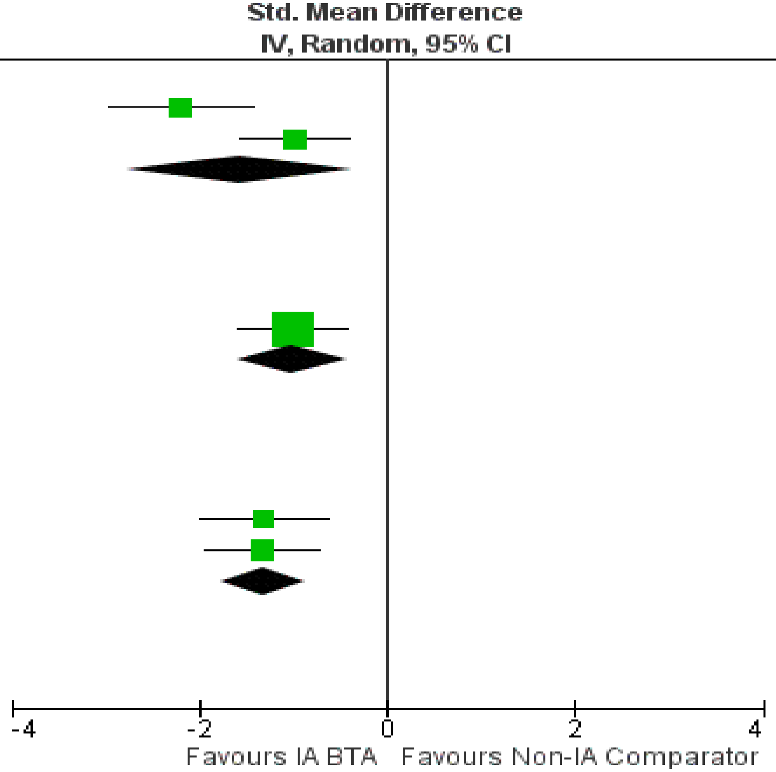
Knee: pain outcomes (vs non-IA comparators)

Study or Subgroup	IA BTA Mean	IA BTA SD	IA BTA Total	Non-IA Comparator Mean	Non-IA Comparator SD	Non-IA Comparator Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.1.1 Short-term								
Hsieh 2016 [34]	2.9	0.9	22	5.4	1.3	21	47.8%	-2.20 [-2.98, -1.43]
Rezasoltani 2021 [29]	3.6	1.6	25	5.3	1.8	25	52.2%	-0.98 [-1.57, -0.39]
Subtotal (95% CI)			**47**			**46**	**100.0%**	**-1.57 [-2.76, -0.37]**
Heterogeneity: Tau² = 0.62; Chi² = 6.07, df = 1 (P = 0.01); I² = 84%								
Test for overall effect: Z = 2.57 (P = 0.01)								
6.1.2 Intermediate-term								
Rezasoltani 2021 [29]	3	1.7	25	4.8	1.8	25	100.0%	-1.01 [-1.60, -0.42]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-1.01 [-1.60, -0.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.35 (P = 0.0008)								
6.1.3 Long-term								
Hsieh 2016 [34]	3.3	1.6	21	5.1	1	20	45.1%	-1.32 [-2.00, -0.63]
Rezasoltani 2021 [29]	2.8	1.6	25	5.1	1.8	25	54.9%	-1.33 [-1.95, -0.71]
Subtotal (95% CI)			**46**			**45**	**100.0%**	**-1.32 [-1.78, -0.87]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%								
Test for overall effect: Z = 5.67 (P < 0.00001)								

N=93

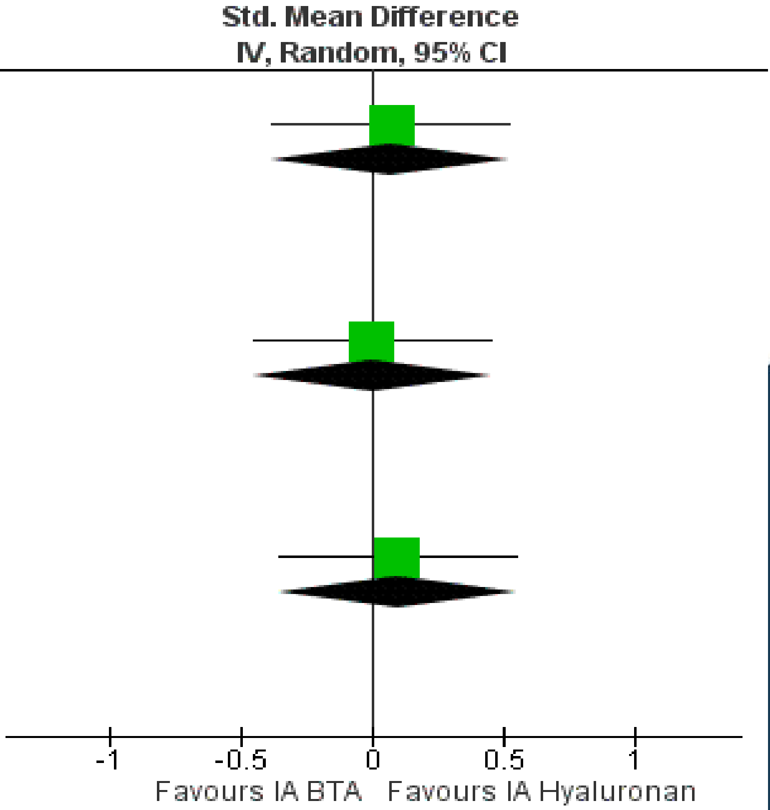
N=50

N=91



Ankle: pain outcomes (vs IA hyaluronan)

		IA BTA			IA Hyaluronan				Std. Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
	1.1.1 Short-term								
	Sun 2014 [38]	1.8	1.3	38	1.7	1.5	37	100.0%	0.07 [-0.38, 0.52]
N=75	**Subtotal (95% CI)**			**38**			**37**	**100.0%**	**0.07 [-0.38, 0.52]**
	Heterogeneity: Not applicable								
	Test for overall effect: Z = 0.31 (P = 0.76)								
	1.1.2 Intermediate-term								
	Sun 2014 [38]	1.7	1.2	38	1.7	1.1	37	100.0%	0.00 [-0.45, 0.45]
N=75	**Subtotal (95% CI)**			**38**			**37**	**100.0%**	**0.00 [-0.45, 0.45]**
	Heterogeneity: Not applicable								
	Test for overall effect: Z = 0.00 (P = 1.00)								
	1.1.3 Long-term								
	Sun 2014 [38]	1.8	0.9	38	1.7	1.1	37	100.0%	0.10 [-0.35, 0.55]
N=75	**Subtotal (95% CI)**			**38**			**37**	**100.0%**	**0.10 [-0.35, 0.55]**
	Heterogeneity: Not applicable								
	Test for overall effect: Z = 0.43 (P = 0.67)								

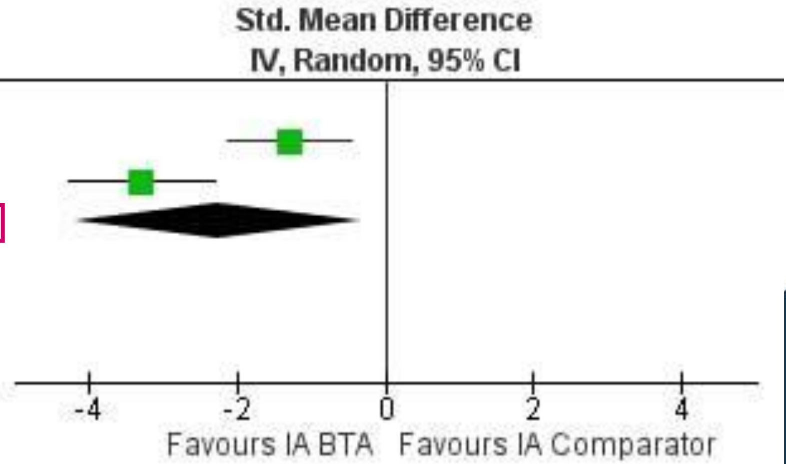


Shoulder: pain outcomes (vs IA GC or anesthetic + saline)

N=68

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
4.1.1 Short-term								
Joo 2013 [36]	3.8	0.6	15	4.6	0.6	13	50.9%	-1.29 [-2.12, -0.47]
Singh 2009 [37]	4.4	0.7	18	6.4	0.5	22	49.1%	-3.28 [-4.26, -2.30]
Subtotal (95% CI)			**33**			**35**	**100.0%**	**-2.27 [-4.21, -0.32]**

Heterogeneity: Tau² = 1.76; Chi² = 9.19, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 2.29 (P = 0.02)



Comments
Heterogeneous conditions: OA, RA, frozen shoulder
Heterogenous IA comparators

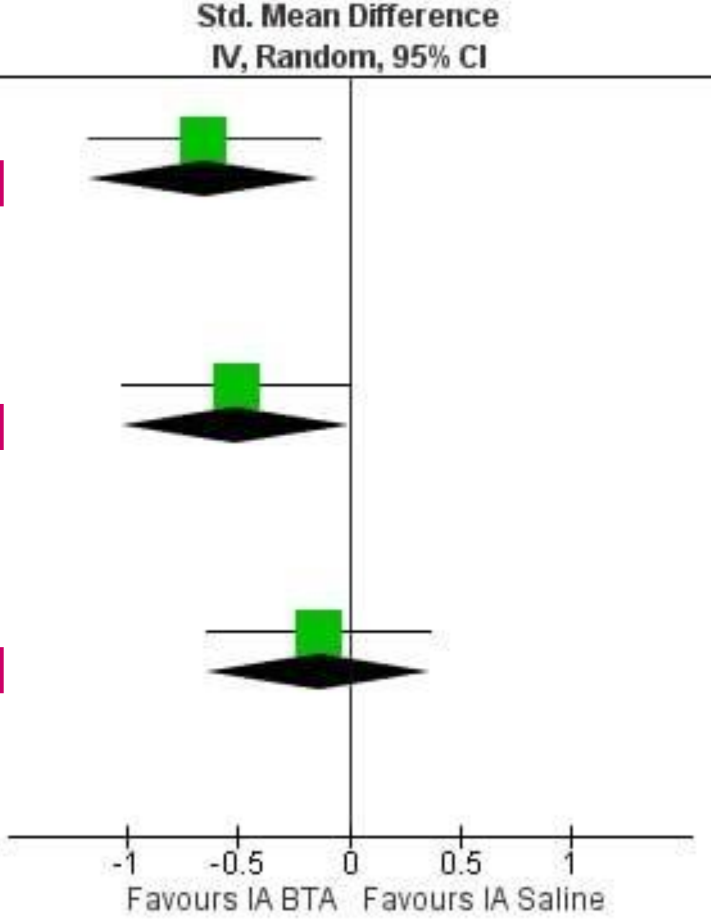
Base-of-the-thumb: pain outcomes (vs IA saline)

Study or Subgroup	IA BTA Mean	IA BTA SD	IA BTA Total	IA Saline Mean	IA Saline SD	IA Saline Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Short-term								
Nguyen 2022 [39]	27.3	17.4	30	40.3	21.3	30	100.0%	-0.66 [-1.18, -0.14]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.66 [-1.18, -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.48 (P = 0.01)								
2.1.2 Intermediate-term								
Nguyen 2022 [39]	36	23	30	48.7	25.8	30	100.0%	-0.51 [-1.03, 0.00]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.51 [-1.03, 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.95 (P = 0.05)								
2.1.3 Long-term								
Nguyen 2022 [39]	43.3	23.98	30	46.7	25.1	30	100.0%	-0.14 [-0.64, 0.37]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.14 [-0.64, 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.60)								

N=60

N=60

N=60



Nguyen C et al, Lancet Rheumatol 2022

In summary: effects of IA BoNT/A on pain (vs IA comparators)

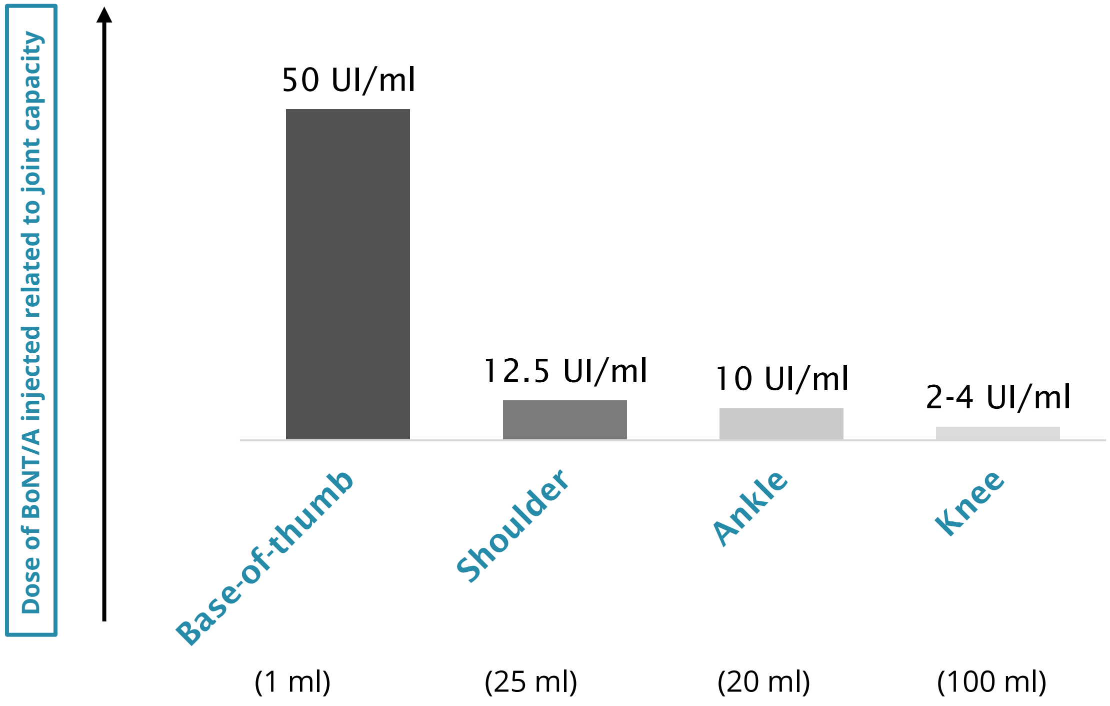
	Short term	Intermediate term	Long term	Comments
Knee	-	-	-	6 RCTs, N > 500
Ankle	-	-	-	1 small RCT
Shoulder	+	NR	NR	2 small RCTs Heterogeneous conditions
Base-of-thumb	+	+	-	1 small RCT

Adverse events ?

- Reported only in 4/14 RCTs
- **Serious adverse events** = 0
- **Minor adverse events** = no imbalance between IA BoNT/A and comparators

Discussion and perspectives

- **IA BoNT/A may reduce shoulder and base-of-the-thumb pain, but not knee or ankle pain**
- **Inconsistent results between joint locations may be explained by 3 key differences**
  - Small vs large studies
  - Weight- vs non-weight-bearing joints
  - Small vs large joints ➔ heterogeneous doses of BoNT/A injected **related to joint capacity**



Base-of-thumb **12.5 to 25 times higher** than knee !

Future directions ➔ the 4 Ds
Dose, **D**ilution, **D**iffusion, **D**uration

Ackowledgements

Principal investigator

Dr. Mathieu Gagnière

Supervisor

Prof. Christelle Nguyen

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Radiologists

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Prof. Antoine Feydy

Dr. Henri Guerini

Thank you

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