Les traitements topiques

une révolution dans le traitement des douleurs neuropathiques périphériques

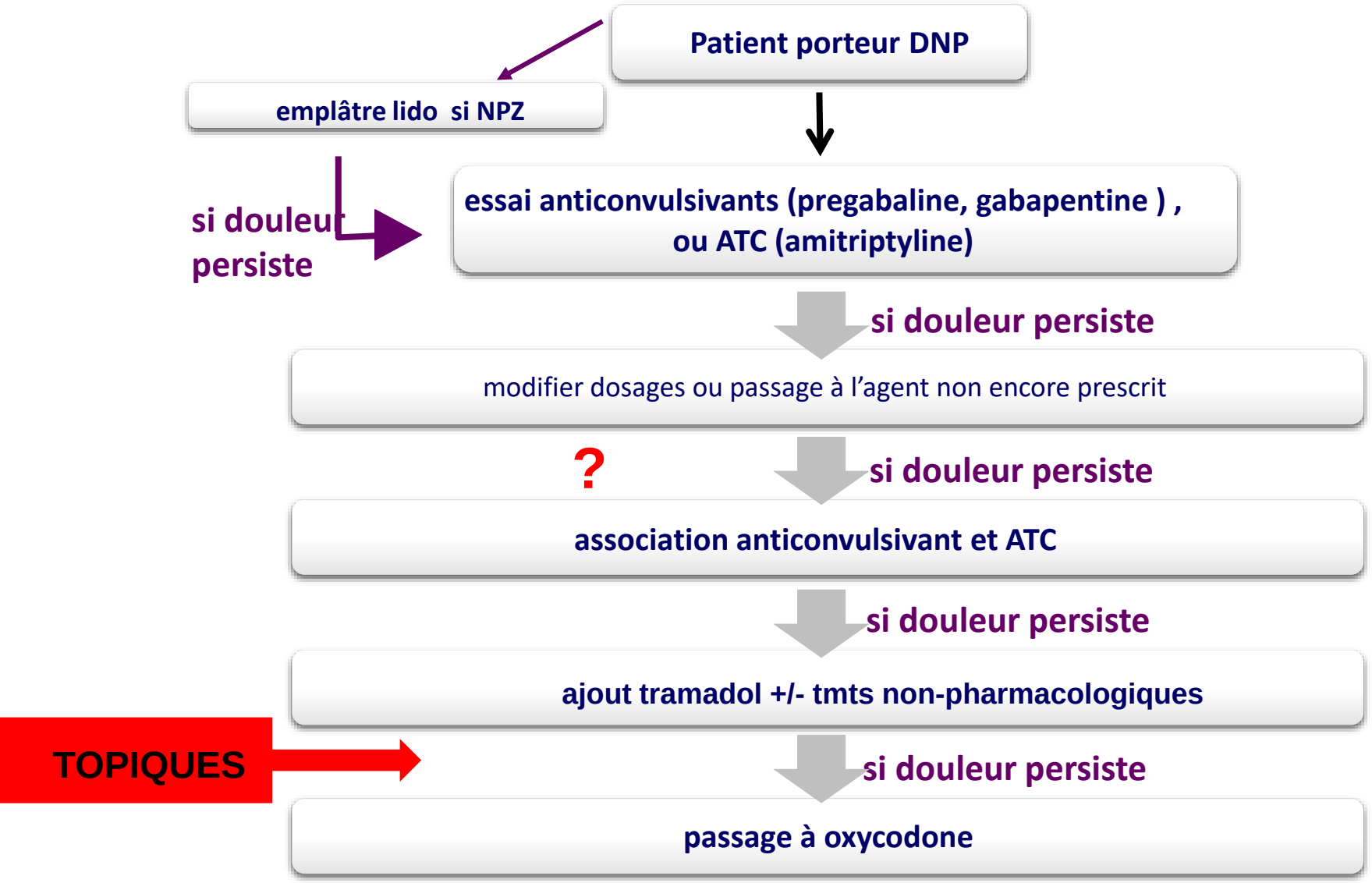
capsaïcine haute concentration, toxine botulique …

Nouvelles Recommandations

Pr. Éric VIEL, M.D., PhD,
Centre d'Évaluation et de Traitement de la Douleur
Centre Hospitalier Régional Universitaire Caremeau

cemd Collège des Enseignants de Médecine de la Douleur
MUSE MONTPELLIER UNIVERSITY of EXCELLENCE
inm institute for neurosciences montpellier
INSTITUT Analgesia
Université Montpellier 1 FACULTÉ MÉDECINE Montpellier - Nîmes
CHU NÎMES

Dans la “vraie-vie“ , l’algorithme est de mise en oeuvre complexe et parfois approximative : changements et mille-feuilles sont la norme !!!



Impact de la douleur neuropathique et de ses traitements sur le patient

- Reduced quality of life[1]
- General activity[1]
- Relationships[2]
- Reduced work status[2]

Quality of life

- Depression[1]
- Anxiety[1]
- Sleep disturbance[1]
- Patient mood[1]

Psychological burden

- 1. Radat F, et al. *Eur J Pain* 2013;17:1547-1557. 2. Liedgens H, et al. *ClinicoEconomics and Outcomes Research* 2016;8:113-126.

EXPERT OPINION

Expert Opinion on Pharmacotherapy

Cesare Bonezzi, Amedeo Costantini, Giorgio Cruccu, Diego M.M. Fornasari, Vittorio Guardamagna, Vincenzo Palmieri, Enrico Polati, Pierangelo Zini & Anthony H Dickenson

(2020) 21:11, 1377-1387

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

Capsaicin 8% dermal patch in clinical practice: an expert opinion

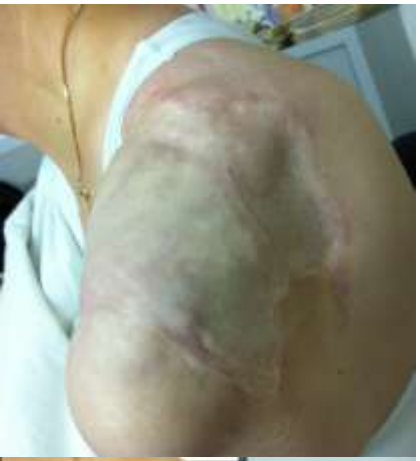
Table 6. Risk of adverse events for the different oral agents in comparison to placebo, data taken from [68].

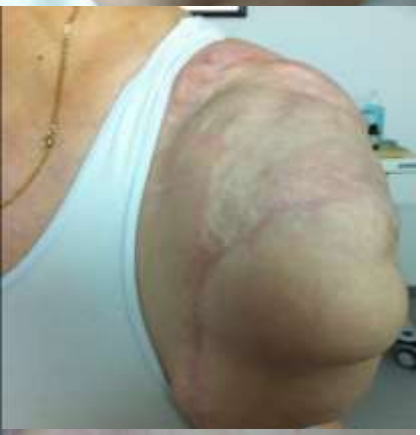
Adverse event	Oral agent	Risk vs placebo; OR (95% CI)
Somnolence	Gabapentin	4.03 (95% CI:2.36–6.57)
	Pregabalin	4.14 (95% CI:3.00–5.60)
	Duloxetine	3.54 (95% CI:2.51–4.90)
	Amitriptyline	147.73 (95% CI:5.91–596.83)
Dizziness	Gabapentin	4.69 (95% CI:2.83–7.55)
	Pregabalin	4.63 (95% CI:3.44–6.16)
	Duloxetine	1.92 (95% CI:1.37–2.65)
	Amitriptyline	31.13 (95% CI:2.76–141.00)
Fatigue	Gabapentin	3.73 (95% CI:0.98–11.10)
	Pregabalin	2.21 (95% CI:0.25–8.98)
	Duloxetine	2.64 (95% CI: 1.32–4.95)
Discontinuation due to adverse events	Gabapentin	2.2 (95% CI:1.36–3.41)
	Pregabalin	2.03 (95% CI:1.5–2.71)
	Duloxetine	2.35 [95% CI, 1.68–3.2)]

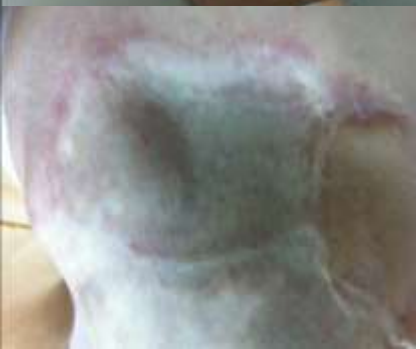
compliance thérapeutique???

Françoise G., 55 ans
section traumatique MSG
douleurs fantômes & moignon

55 ans, AVP bus/ravin dans les Pyrénées
Arrachement MSG/ 27 mois plus tôt



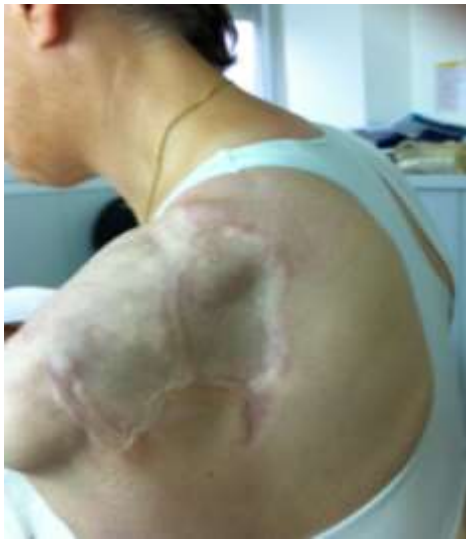




Abandon traitements systémiques (dont opioïdes, prégabaline)

Décision : patch capsaïcine d'emblée
4 applications / 9 mois

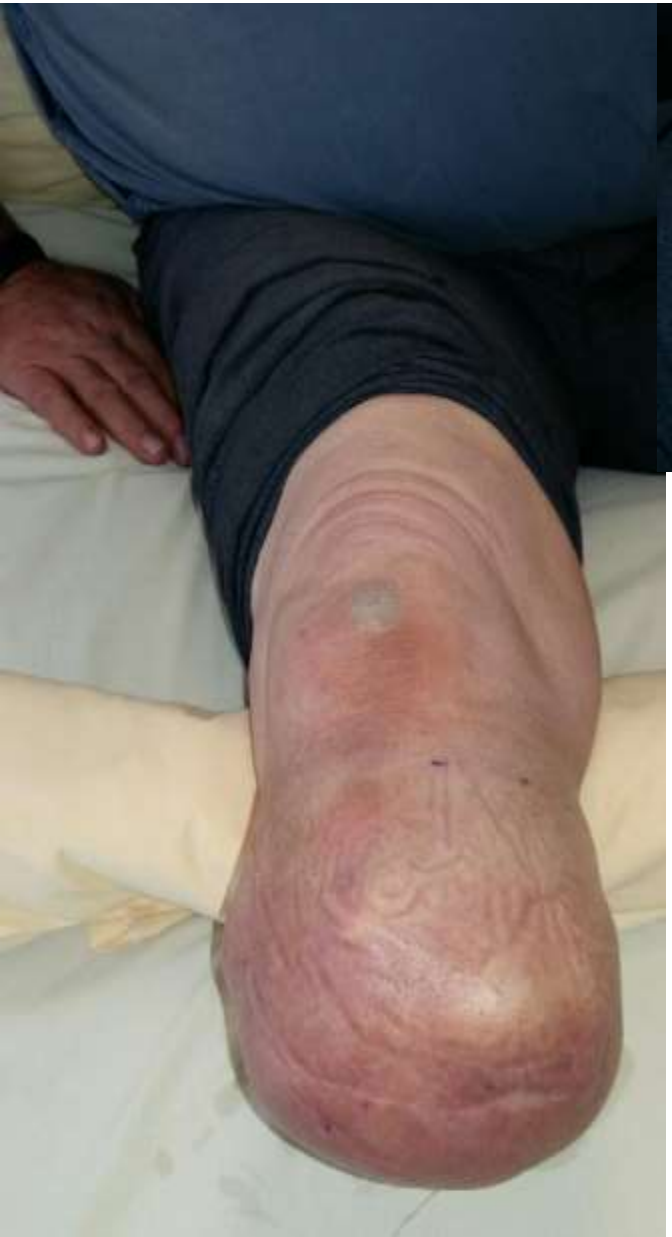
Successivement :
- → disparition des ADP
- → réduction surface allodynie et DNP
- → réduction intensité

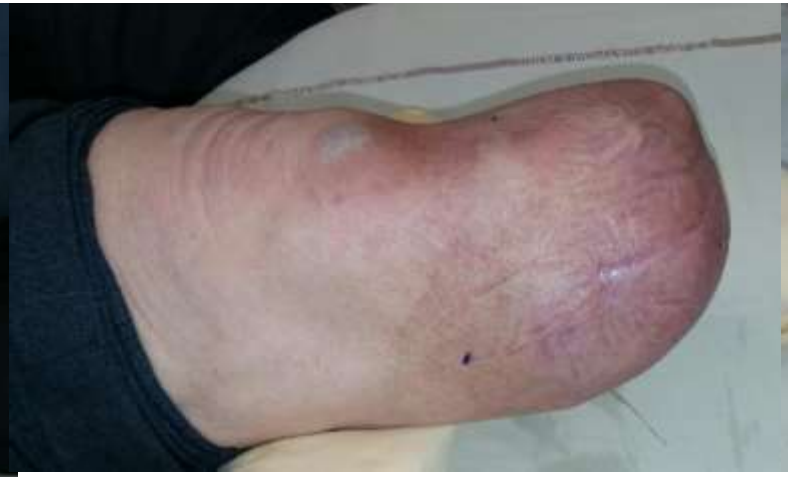


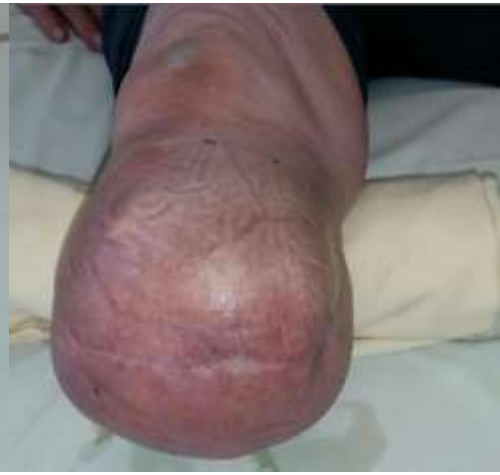
Injection BoNT sur zones gâchettes cicatrices

Totalement asymptomatique 11 mois après début traitement
(douleur et effets adverses / prises médicamenteuses)

Gérard L., 48 ans
Amputation chirurgicale
Douleurs moignons & fantôme douloureux







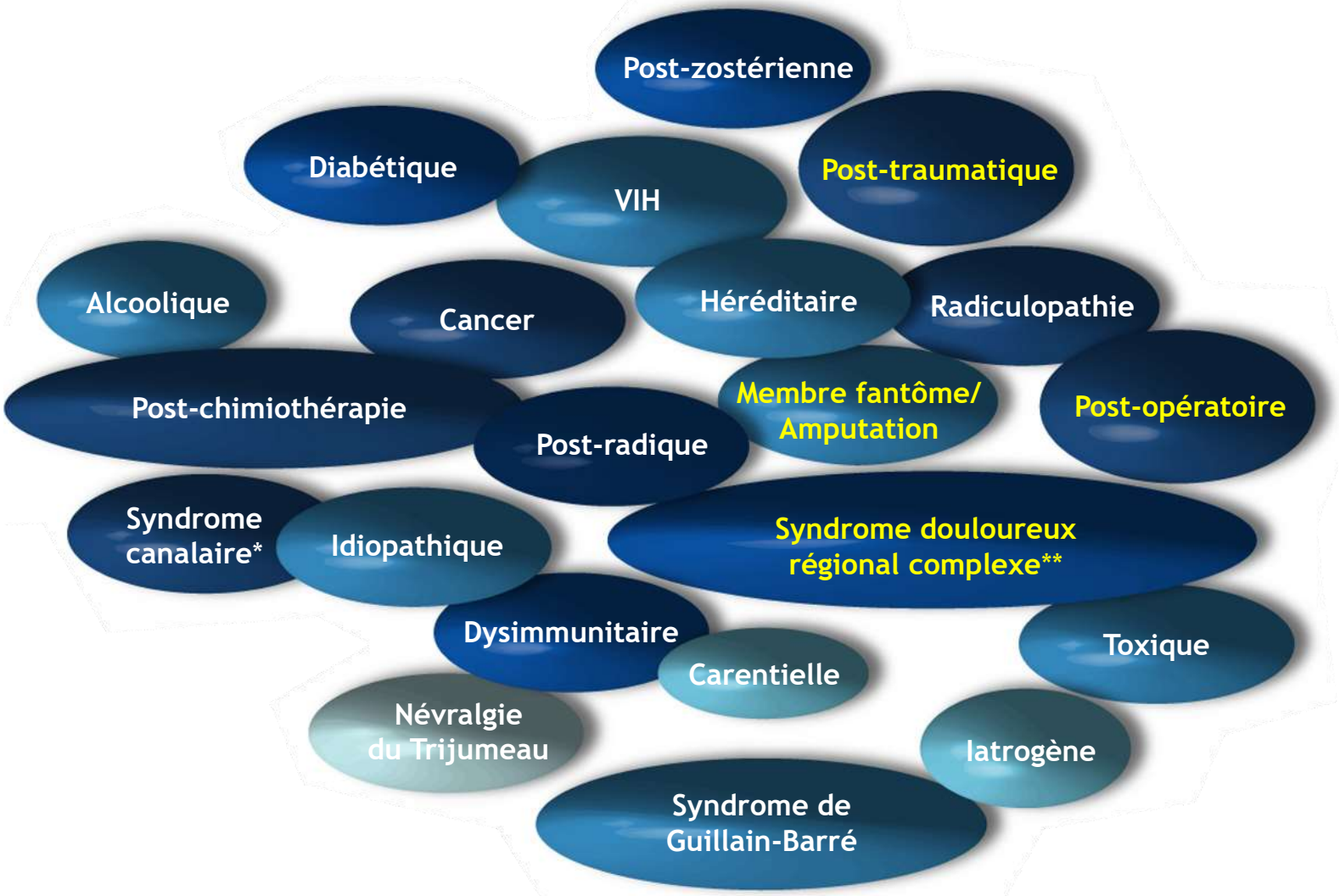
H 48 ans, AOMI, diabète insulino-requérant peu équilibré (HbA1c 11,8%)
Tabagisme sévère, 35 PA, dyslipidémie,
Amputation trans-tibiale 8 ans auparavant
DNP/ moignon + ADP> 10-15 /jr
Traitements systémiques peu efficaces

3 applications / 7 mois → soulagement complet

malgré alccolo-tabagisme persistant et diabète non équilibré

Récidive tous les 5 mois environ

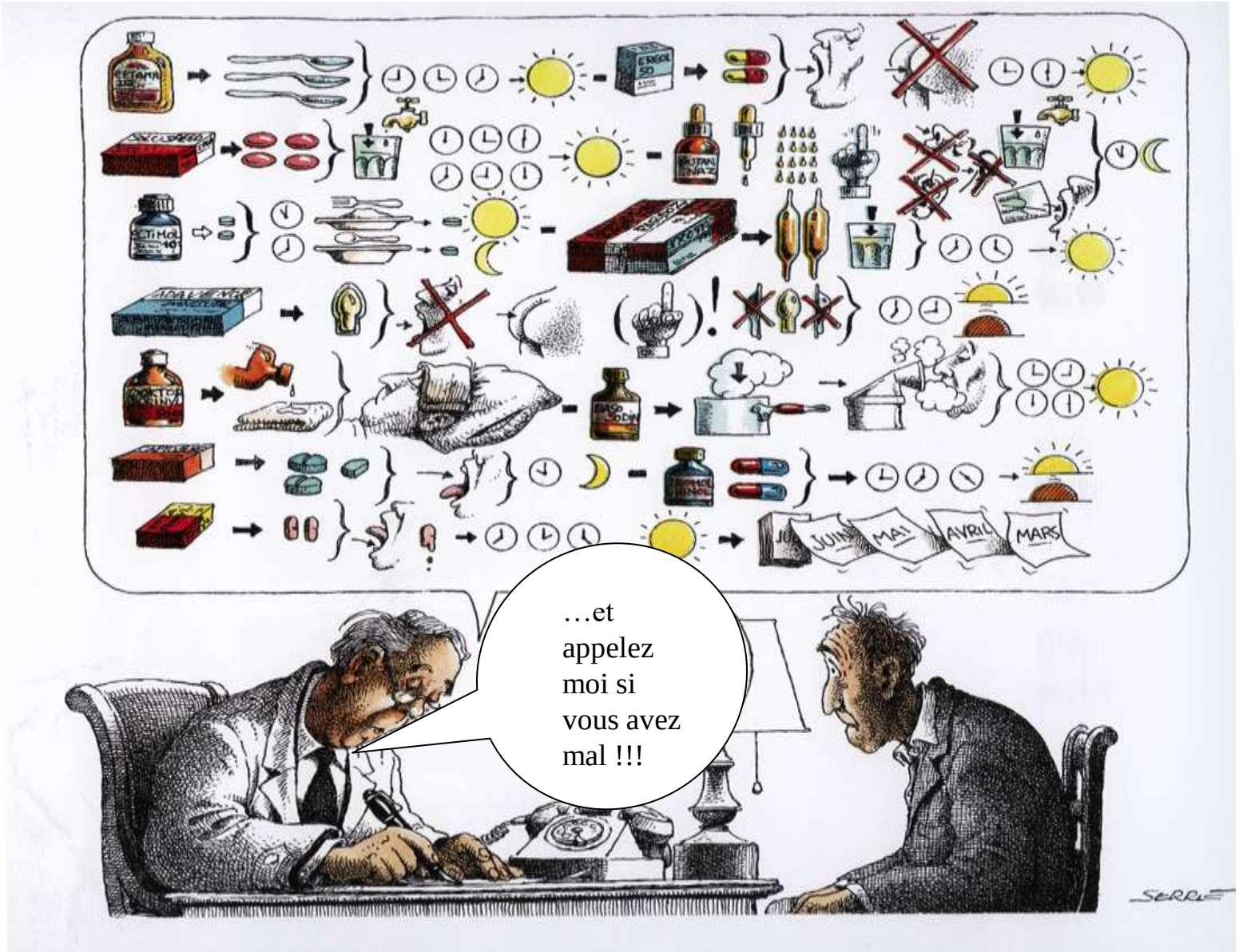
Principales étiologies des DNP (1,2)



** Ex. : syndrome du canal carpien, du canal tarsien, etc. - ** Atteintes des nerfs ou plexus d'origine traumatique ou chirurgicale -*

(1) Attal N, Bouhassira D. Neuropathies périphériques douloureuses in Bouche P et al. Neuropathies périphériques. Doin Eds 2004 : 355-79.
(2) Dworkin RH et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 ; 60 (11) : 1524-34.

des traitements variés, parfois … inattendus



observance thérapeutique ???

Unmet needs

- Existing therapies for neuropathic pain are not effective for the majority of patients, only 1/4 patients find relief which is generally only 50% reduction in pain[10]
- Current treatments for neuropathic pain are symptomatic rather than disease modifying or curative[10]
- Treatments may act preferentially or selectively on some components of the aetiological diagnosis, and don't have a uniform and global effect[8]
- Combination therapy with 2 or more drugs may be required[8]
- There is a frequent need for at least one drug therapy for side effects of core therapies and at least one drug therapy for psychological non-pain suffering[8]
- The need to be aware of additive and synergistic effects as well as drug-drug interactions[8]

10. Backonja M and Woolf CJ. *The Oncologist* 2010;15(suppl 2):24-29. 8. Harden N and Cohen M. *J Pain Symptom Manage* 2003;25:S12-S17.

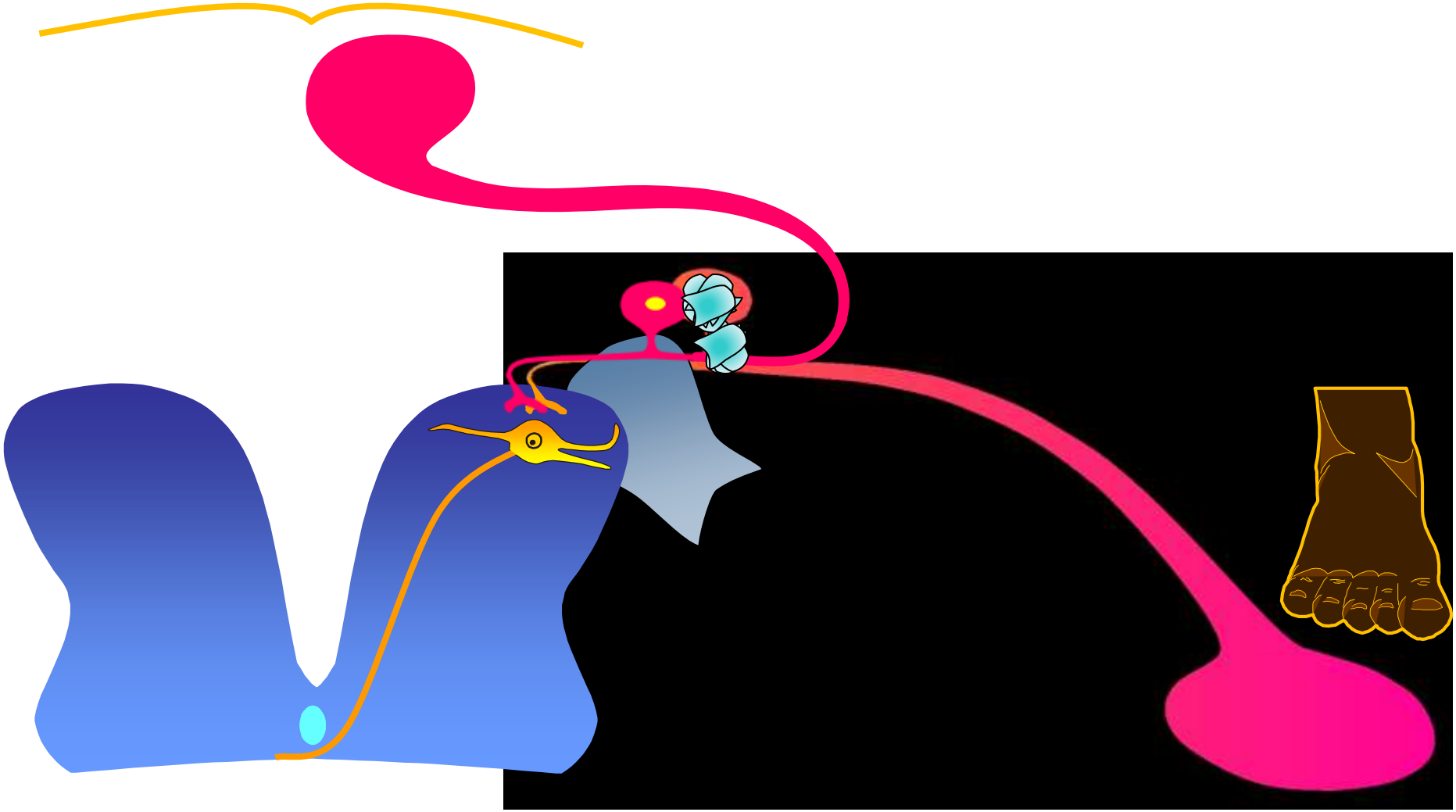
Toxine botulique A

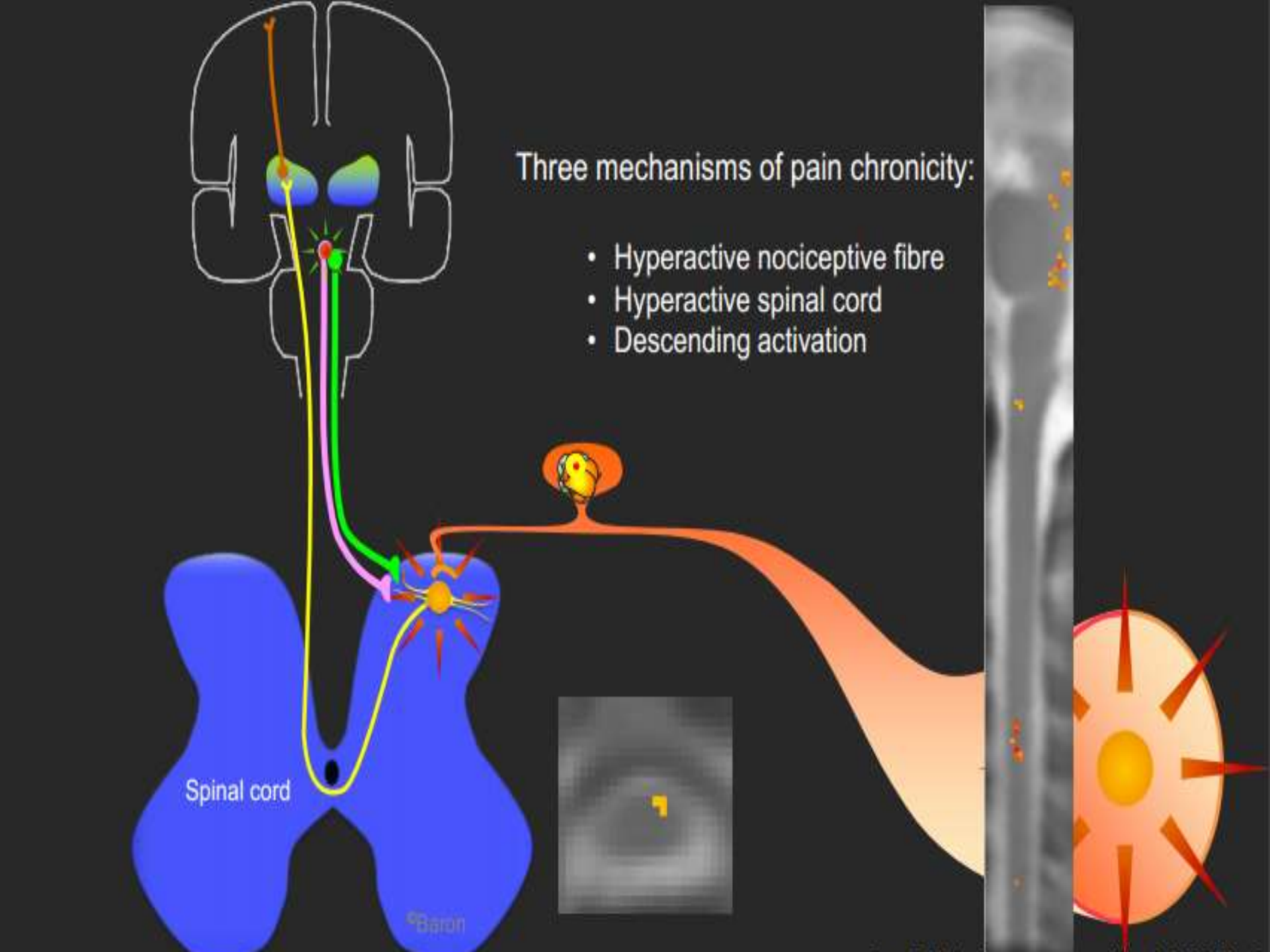
Patch de capsaïcine

Quel rationnel pour l'utilisation topique de la capsaïcine pour traiter la douleur neuropathique périphérique ? Comment çà marche ?

Une vieille histoire … qui commence avec les médecins arabo-andalous *Ibn SIna* et *Ibn Roshd* ! et l'application topique de *felfel soudaniya*

Mécanismes : sensibilisation périphérique, sur-expression canaux TRPV1




Three mechanisms of pain chronicity:
• Hyperactive nociceptive fibre
• Hyperactive spinal cord
• Descending activation
Spinal cord
©Baron

The capsaicin receptor: a heat-activated ion channel in the pain pathway

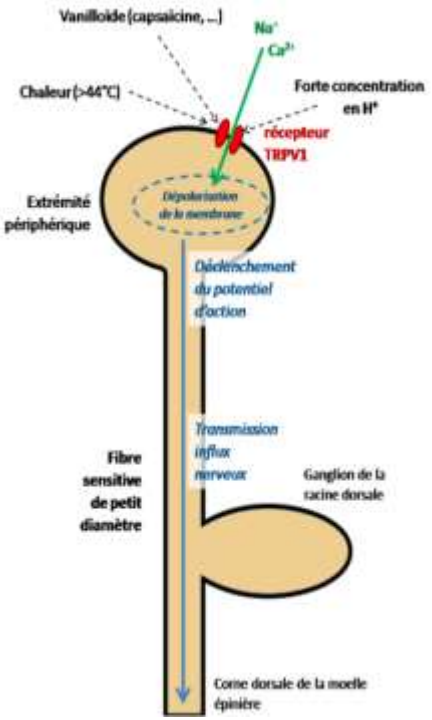
Nature **389**, 816–824 (1997)

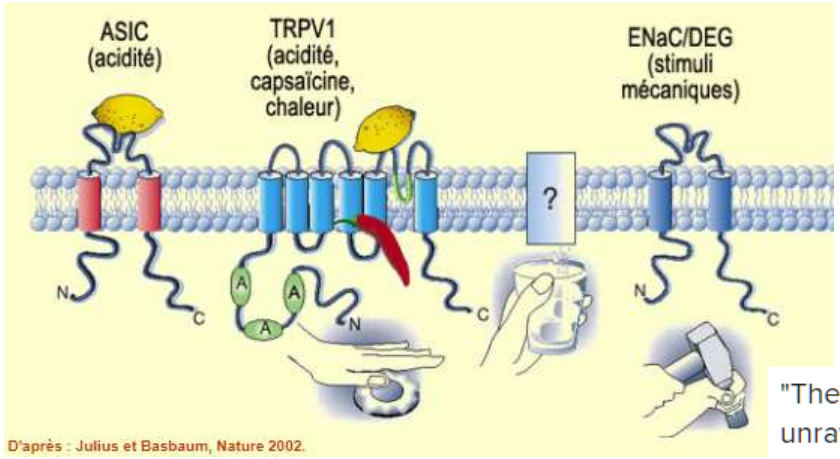
Michael J. Caterina, Mark A. Schumacher, Makoto Tominaga, Tobias A. Rosen, Jon D. Levine & David Julius

The Nobel Assembly at the Karolinska Institute has decided to award the 2021 Nobel Prize in Physiology or Medicine to

DAVID JULIUS
ARDEM PATAPOUTIAN

"for their discoveries of receptors for temperature and touch"

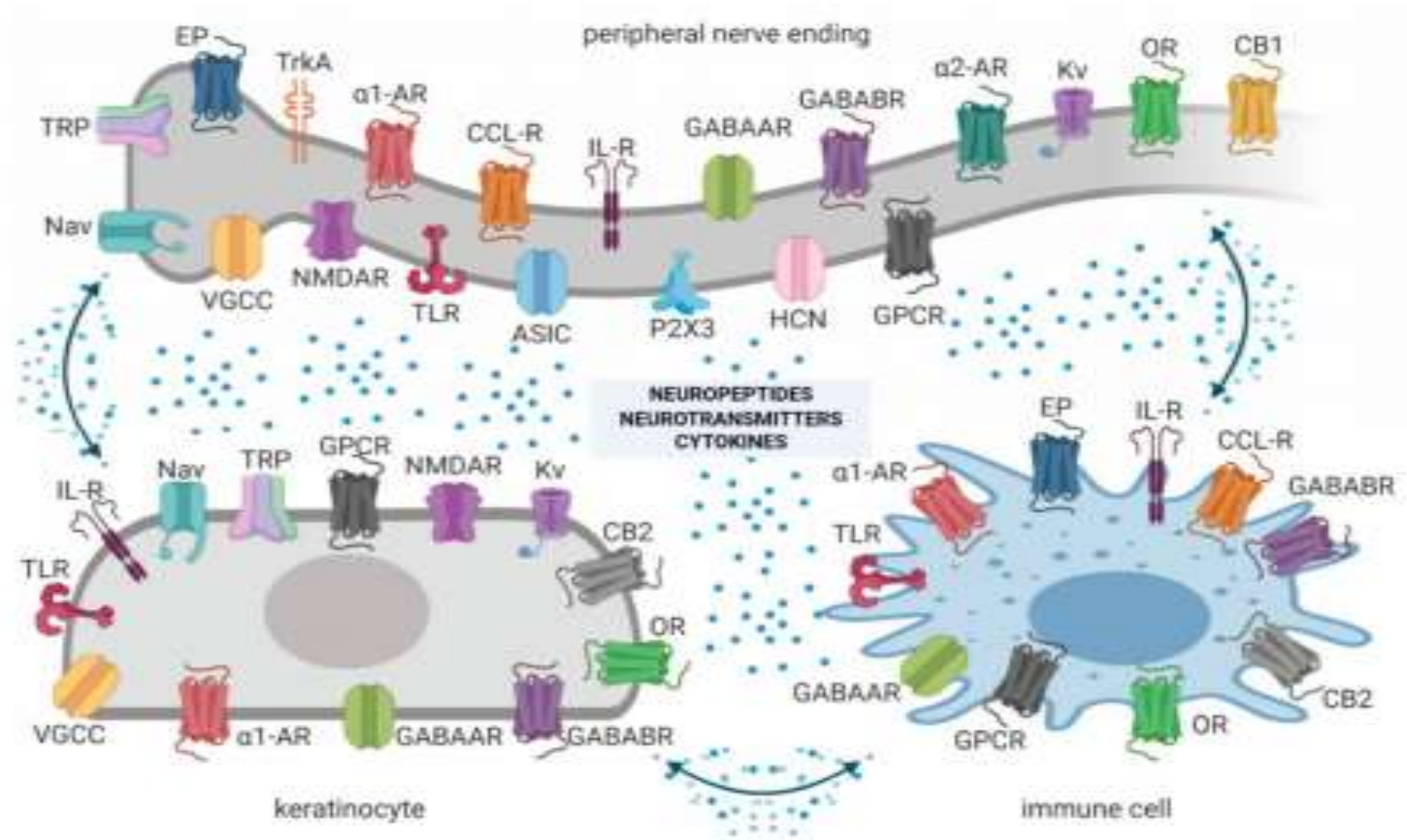




D'après : Julius et Basbaum, Nature 2002.

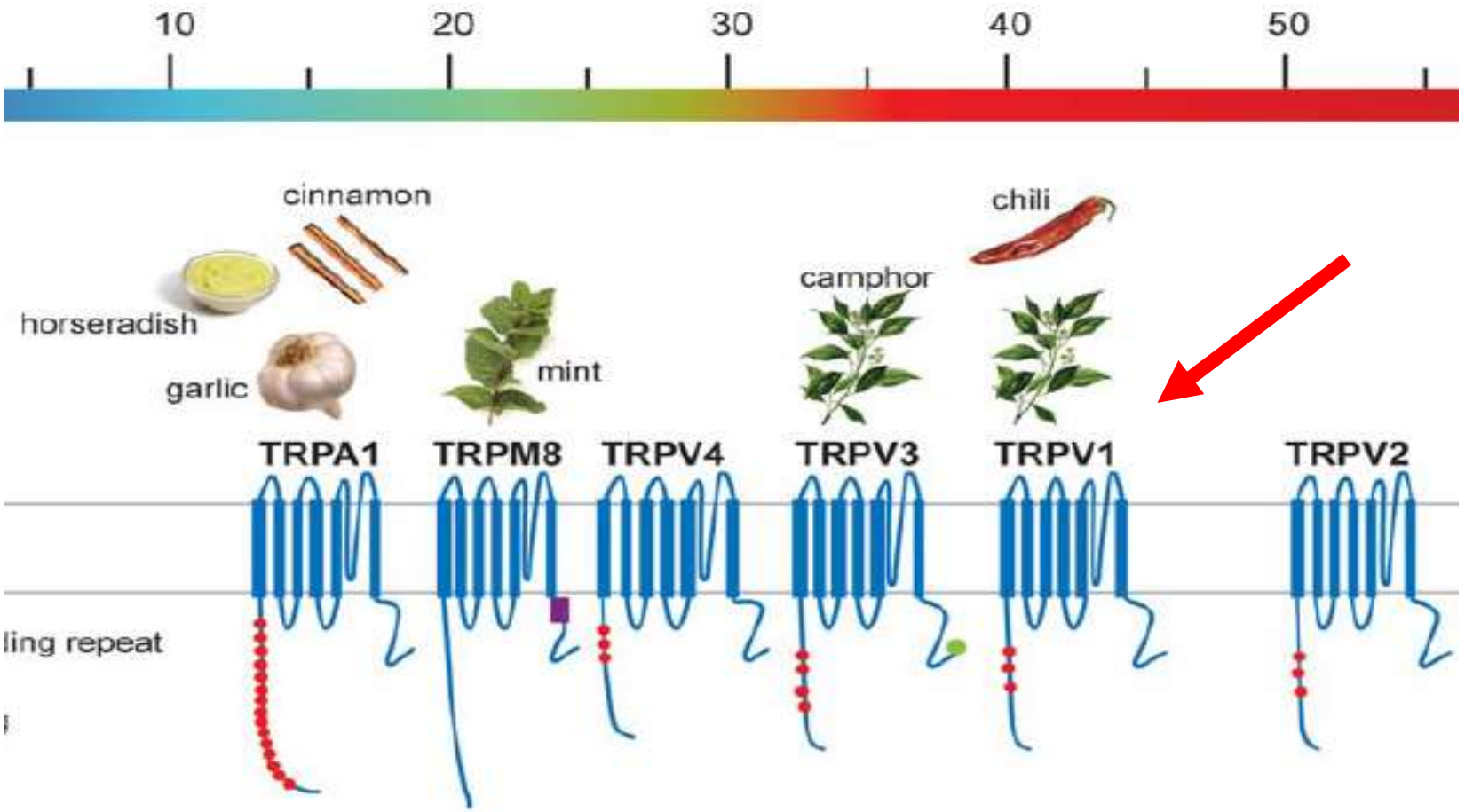
"The discovery of TRPV1 was a major breakthrough leading the way to the unravelling of additional temperature-sensing receptors," the committee said.

Rôle des récepteurs TRPV1



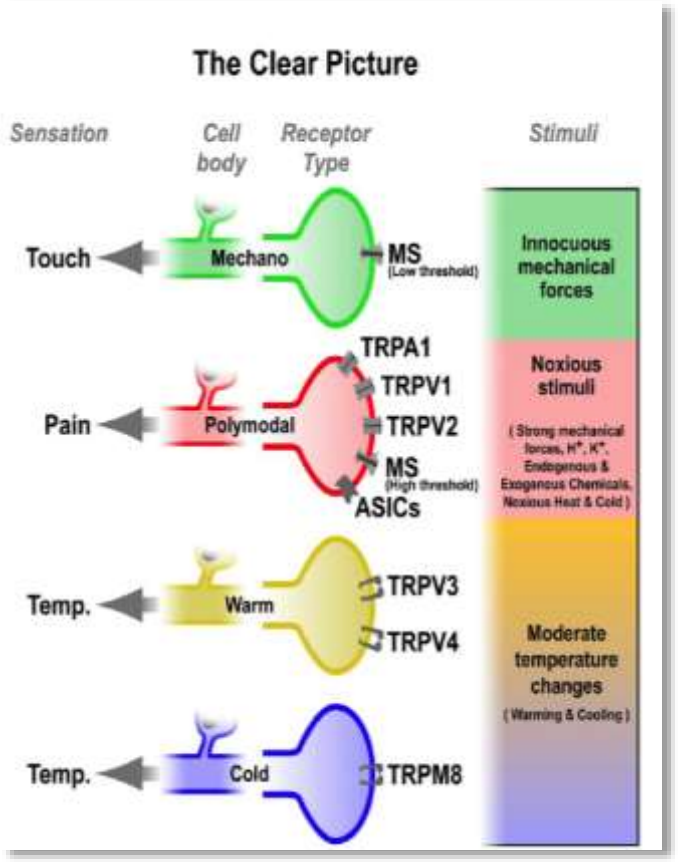
des nocicepteurs spécifiques de ligands naturels des traitements topiques connus…

Thermorégulation

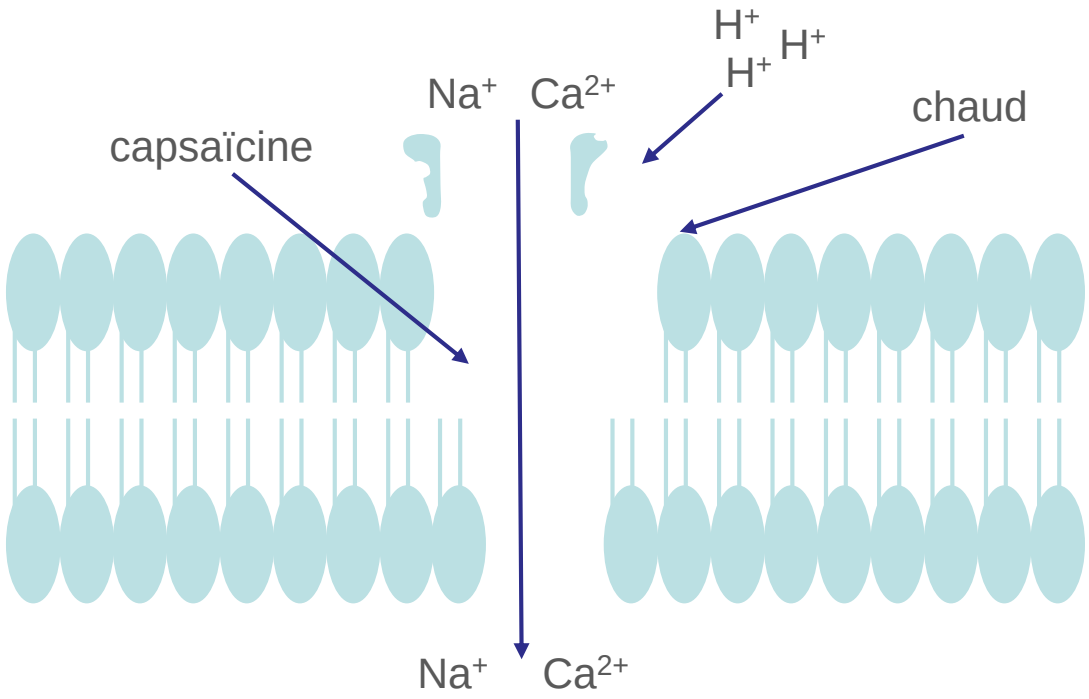


Dhaka (2006) Annu. Rev. Neurosci.

la capsaïcine n'est pas un antagoniste … mais un agoniste des récepteurs TRPV1

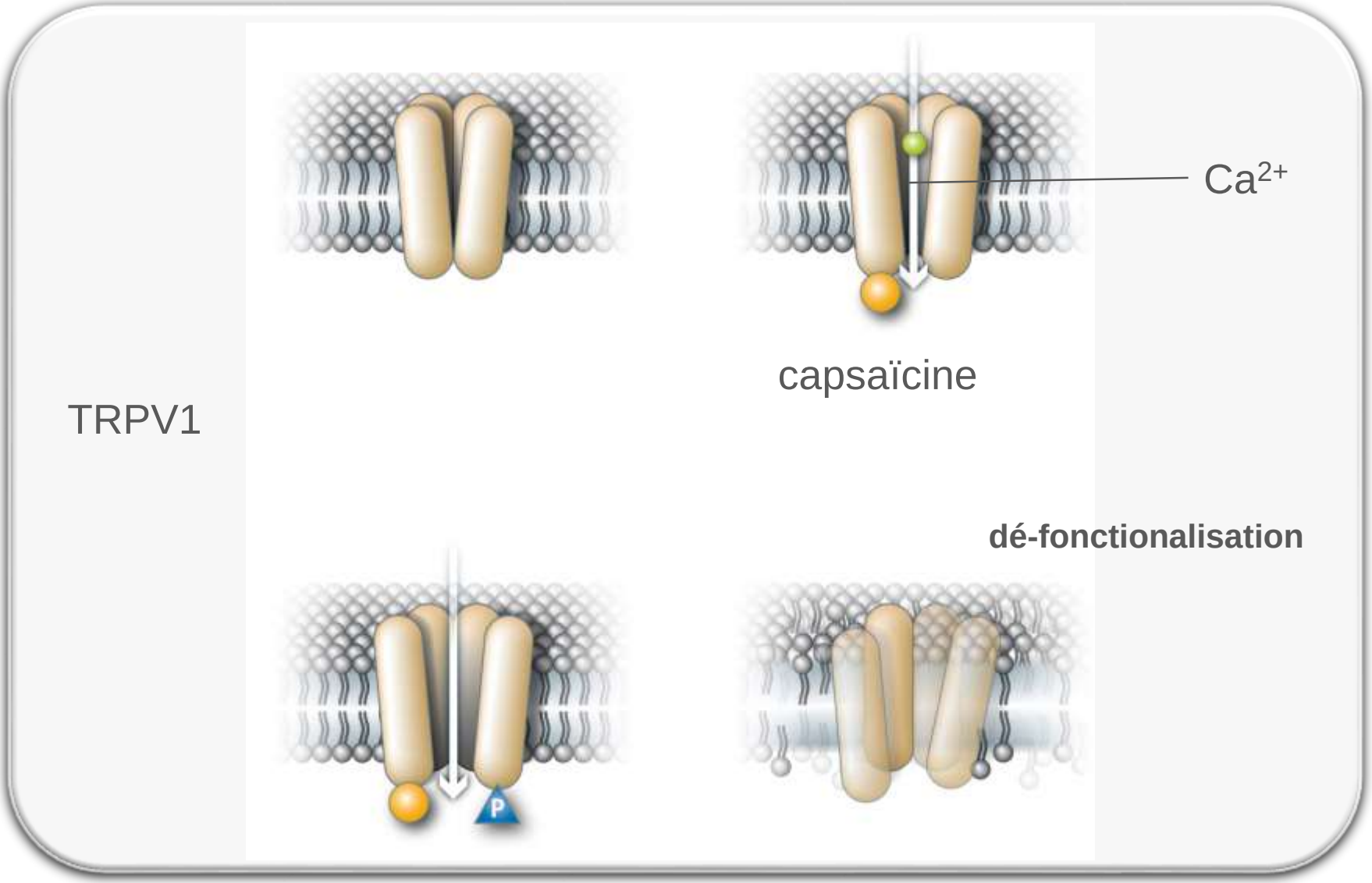


Belmonte and Vania, Mol Pain, 2008



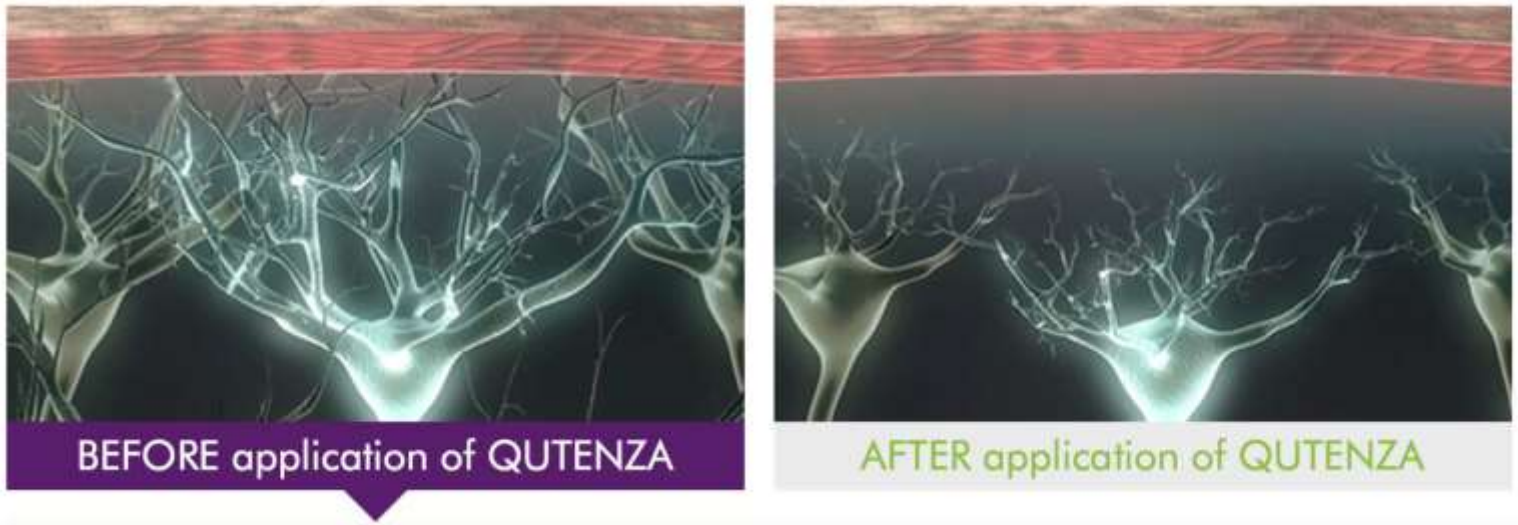
Tominaga and Julius 2001

la capsaïcine est un agoniste des récepteurs TRPV1



Qutenza has a highly selective mode of action

Schematic representation of nerve fibre retraction



- In peripheral neuropathic pain, nociceptor fibres are hyperactive and hypersensitive[2]
- Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor, commonly expressed on nociceptive fibres[1,2]
- TRPV1 receptors are usually activated by temperature, pH and endogenous agonists[2]

TRPV1, transient receptor potential vanilloid 1.

1. Qutenza Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/573/smpc. Accessed October 2019. 2. Anand P and Bley K. *Brit J Anaesth* 2011;107:490-502.

Local or systemic treatment for Neuropathic Pain? ELEVATE: an open-label, randomized, multicenter, non-inferiority efficacy and tolerability study.

Maija Haanpaa (1), Etienne Ernault (2), Tommaso Siciliano (3)

1. Departments of Anaesthesiology and Neurosurgery, Pain Clinic, Helsinki University Hospital, Helsinki, Finland. 2. Astellas Pharma Europe, BV, The Netherlands. 3. Astellas Pharma Europe, Chertsey, UK

Peripheral Neuropathic Pain (PNP) is highly prevalent in the world. PNP has a devastating impact on patients' lives and it poses a high burden on healthcare resources. Topical high concentration (8%) capsaicin patch (QUTENZA™) and oral Pregabalin are effective treatments for PNP. QUTENZA™ is licensed in Europe for the treatment of NP in non-diabetic adults.

METHODS

568 subjects were randomized to one of two treatment arms: QUTENZA™ (single application of up to 4 patches) or Pregabalin (daily administration at a flexible, optimized dose). All subjects recorded average pain scores for 8 weeks: daily, for the first two and for the last week of treatment, otherwise weekly. The primary efficacy endpoint was the proportion of subjects in each arm who achieved at least a 30% decrease in the average NPRS score from Baseline to Week 8. Safety was assessed by evaluation of adverse events, laboratory tests and vital signs. Hypotheses were tested using odds ratio. A non-inferiority margin of -8.5%, under reasonably conservative assumptions, translated into a margin on the odds ratio (OR) of 0.693. The null hypothesis of inferiority was rejected if the two-sided 95% confidence interval for the odds ratio of QUTENZA™ versus Pregabalin fell completely above 0.693.

568 subjects were randomized to one of two treatment arms: QUTENZA™ (single application of up to 4 patches) or Pregabalin (daily administration at a flexible, optimized dose). All subjects recorded average pain scores for 8 weeks

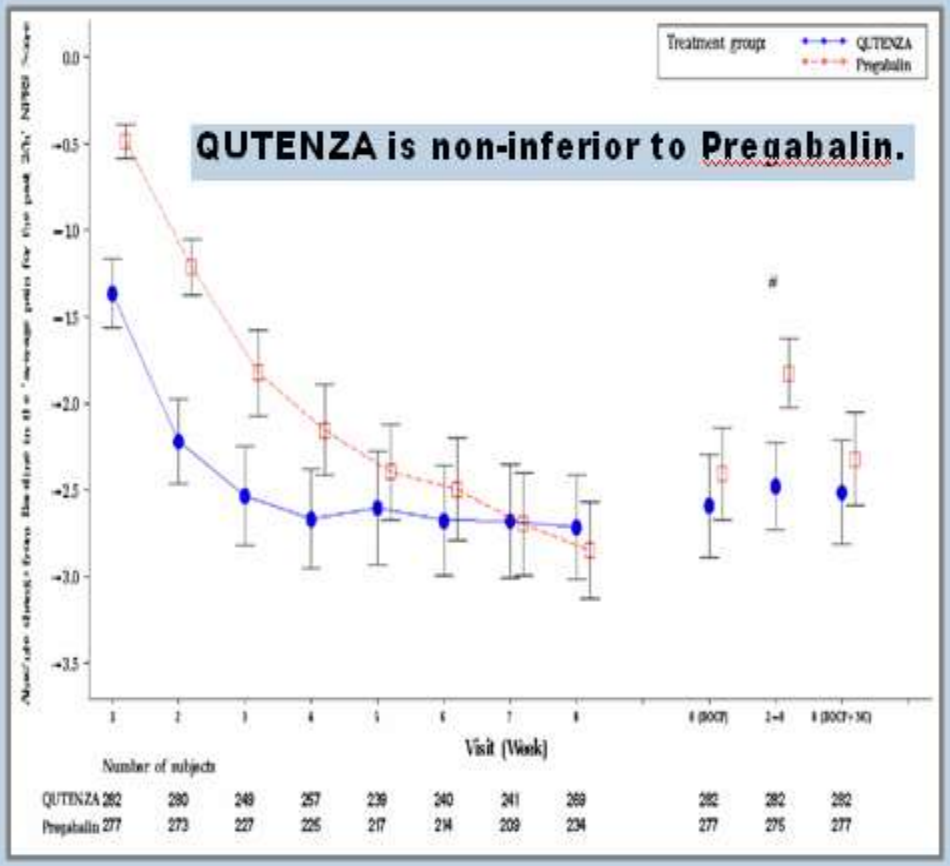
RESULTS

In both the Full Analysis Set (FAS - all randomised subjects who initiated treatment) and the Per Protocol Set (PPS - subset of subjects of the FAS, selected to ensure sensitivity to differences in treatment effects), the lower bound for the 95% confidence interval for the odds ratio of QUTENZA™ versus Pregabalin was greater than 0.693

Difference (QTZ - Pregabalin)	-1.2%		-0.3%
95% CI for Difference	(-7.1%, 4.4%)		(-6.3%, 6.0%)
Adverse Non-Inferiority criteria?	No		No
P-value for superiority test	p=0.866		p=0.957

95% CI for the difference between Qutenza and Pregabalin was above -8.5%
Results on FAS and PPS demonstrated that QUTENZA is non-inferior to Pregabalin.

Mean Percent Change from Baseline in the Average NPRS Score throughout the Study (FAS)



TIME TO ONSET OF PAIN RELIEF IN ELEVATE: AN OPEN-LABEL, RANDOMISED, MULTICENTER NON-INFERIORITY EFFICACY AND TOLERABILITY STUDY

Maija Haanpaa (1), Etienne Ernault (2), Tommaso Siciliano (3)

WIP meeting Maastricht mai 2014

Peripheral Neuropathic Pain (
devastating impact on patient
poses a high burden on health
Topical high concentration (8%
(QUTENZA™) and oral pregaba
treatments for PNP.[2,3] ELEVATE
randomised Clinical Trial to co
and tolerability of these drugs
PNP.

Table 2. Treatment emergent adverse events

Preferred Term (MedDRAV 13.1)	Qutenza™ (N=282)	Pregabalin (N=277)
Application site pain	67 (23.8%)	0
Erythmia	59 (20.9%)	1 (0.4%)
Burning sensation	45 (16.0%)	1 (0.4%)
Headache	38 (13.5%)	51 (18.4%)
Application site erythmia	25 (8.9%)	0
Pain	18 (6.4%)	7 (2.5%)
Pain in extremity	15 (5.3%)	9 (3.2%)
Nausea	14 (5.0%)	35 (12.6%)
Abdominal pain upper	9 (3.2%)	15 (5.4%)
Dizziness	7 (2.5%)	54 (19.5%)
Oedema peripheral	3 (1.1%)	17 (6.1%)
Somnolence	2 (0.7%)	43 (15.5%)
Constipation	2 (0.7%)	14 (5.1%)
Vertigo	1 (0.4%)	14 (5.1%)
Weigth increase	0	17 (6.1%)
Dry mouth	0	15 (5.1%)

et its primary endpoint,
QUTENZA™ is as effective
n optimised dose of
s with PNP over 8 weeks.
n relief was significantly
NZA™ arm.

Median time to pain
(where 50% of subje
had a 30% reduction
in 'average pain for t
past 24 hours') was
days (95% CI 6.0, 10
for QUTENZA™ versu
36 days (95% CI 22.
50.0) for pregabalin.
hazard ratio adjusted
country-gender-NPR
at baseline was 1.68
in favour of QUTENZA™
(95% CI 1.35, 2.08),
p<0.0001.

of pain relief

ups QUTENZA™
Pregabalin

ubjects Without Pain Relief)

0%

Study Day

Number of Subjects Remaining at Risk

QUTENZA™	282	141	112	107	87	96	95	94	65	8	3	0
Pregabalin	277	211	163	151	132	117	112	97	63	4	0	0

HR: Hazard ratio

Purpose
performed
tolerability
weight) cu
pared with
balin, gal
patients wi
(PDPN).

Method
LINE, Coc
Service Ce
base of A
ducted to

(OR,
, 1.66
com-
1.79]).
assess
NMA
only
as 0%
agents
h pla-
dulox-
abalin,
nausea
uloxe-
abalin,
prega-
icantly
risk of

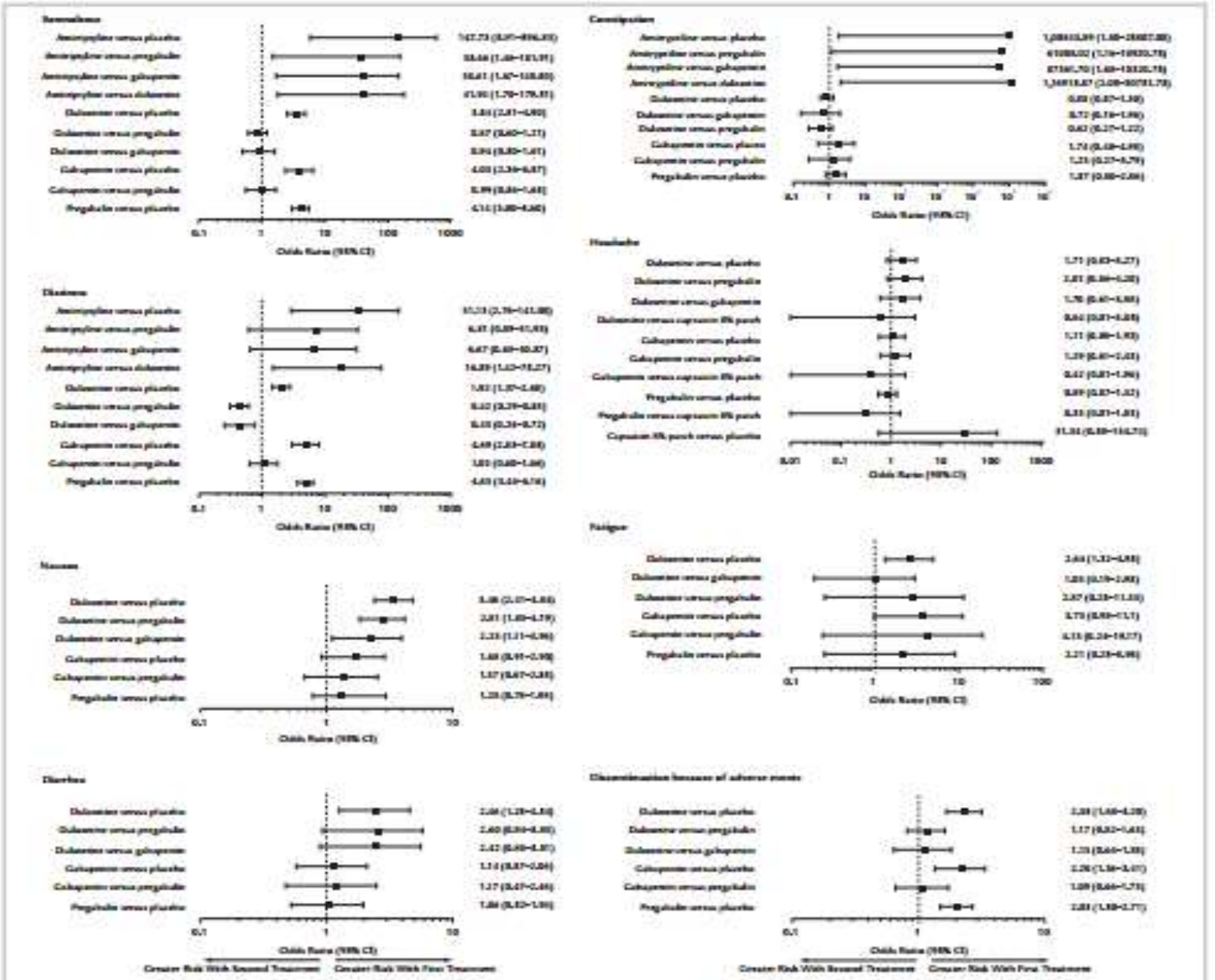
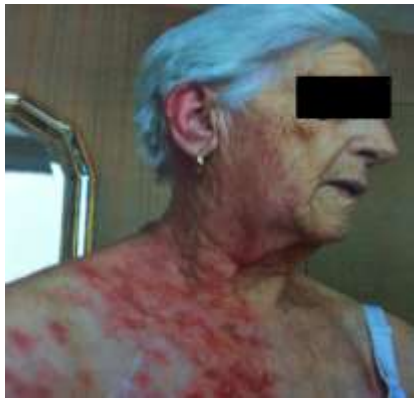


Figure 4. Network meta-analysis (direct and indirect comparisons combined): tolerability outcomes (fixed-effects model).

Treatment impact on patient-reported outcomes in peripheral neuropathic pain: comparing single intervention with topical high-concentration capsaicin to daily oral pregabalin.

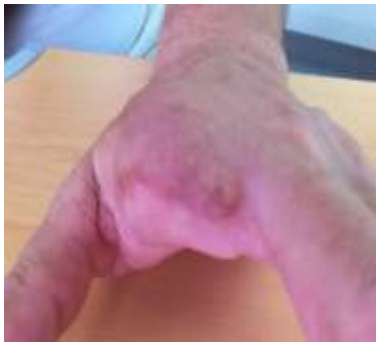
Pain Phys 2021; **E.VIEL**, M.EERDEKENS, P.KANDASWAMY

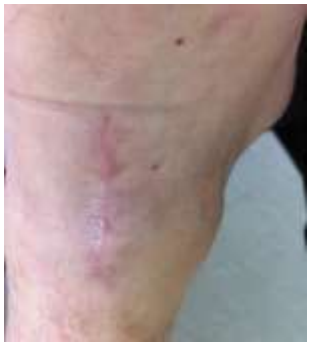


Background: PNP is a complex, subjective experience affecting both physical and psychological aspects of functioning. Assessing patient-reported outcomes (PROs) beyond pain relief is important and aligns with the recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials). Moreover, PRO data are key to clinical decision-making when evaluating treatment options. However, direct comparisons between such options are scarce. High-concentration capsaicin 179 mg (8% w/w) cutaneous patch (HCCP) is applied to the skin at minimum intervals of 90 days under physician supervision; alternative recommended treatments for PNP are mostly orally administered on a daily basis. The ELEVATE study directly compared HCCP with pregabalin and found non-inferior efficacy of HCCP to pregabalin in relieving pain after 8 weeks, with a significantly faster onset of action and fewer systemic side effects.

Objectives: The objective of this analysis was to compare PRO outcomes defined as secondary objectives of the ELEVATE study after a single intervention with HCCP to daily oral pregabalin for 8 weeks.

Results : At Week 8, 76% and 75.9% of patients on HCCP and pregabalin respectively, reported to be very much/much/minimally improved on the PGIC. HCCP application was associated with significant improvements from baseline vs pregabalin in MOS-Cog (mean difference: 4.28 [95% CI: 2.90-5.66], p<0.001), EQ-VAS (3.11 [0.30-5.92]; p=0.030), and TSQM global satisfaction (6.74 [2.29-11.20]; p=0.029), particularly the side-effects dimension (21.23 [17.55-24.94]; p<0.0001). No significant differences in improvements were noted for the MOS-Sleep, TSQM convenience, and EQ-UI.





Conclusions : Single intervention with HCCP showed benefits vs daily pregabalin at Week 8 on several PROs. While HCCP has been approved in the US for PNP treatment in diabetic patients, these observations provide information on how patients perceive the effects of distinct PNP treatments. They are complementing already existing knowledge on efficacy and safety of different treatment options with data on patient preferences and may help identifying the appropriate treatment option in dialogue with the patients and shared decision-making.

Qu'en pensent les patients ?

Pain Physician

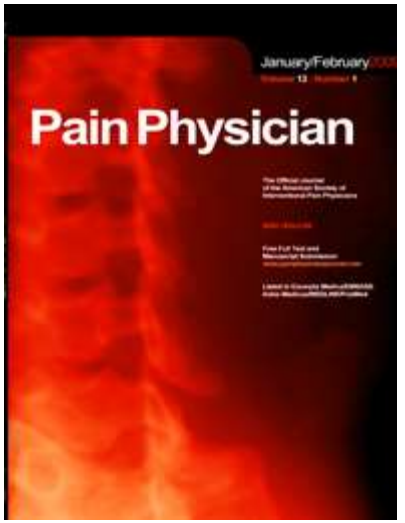
Treatment Impact on Patient-Reported Outcomes in Peripheral Neuropathic Pain: Comparing Single Intervention with Topical High-Concentration Capsaicin to Daily Oral Pregabalin

Background: PNP is a complex, subjective experience affecting both physical and psychological aspects of functioning. Assessing patient-reported outcomes (PROs) beyond pain relief is important and aligns with the recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials). Moreover, PRO data are key to clinical decision-making when evaluating treatment options. However, direct comparisons between such options are scarce. High-concentration capsaicin 179 mg (8% w/w) cutaneous patch (HCCP) is applied to the skin at minimum intervals of 90 days under physician supervision; alternative recommended treatments for PNP are mostly orally administered on a daily basis. Th ELEVATE study directly compared HCCP with pregabalin and found non-inferior efficacy of HCCP to pregabalin in relieving pain after 8 weeks, with a significantly fast onset of action and fewer systemic side effects.
Objectives: The objective of this analysis was to compare PRO outcomes defined as secondary objectives of the ELEVATE study after a single intervention with HCCP to daily oral pregabalin for 8 weeks.
Study design: ELEVATE was an open-label, randomized (1:1) multicenter study.
Setting: The study included 92 sites in 22 countries in Europe and Asia.
Methods : 559 non-diabetic patients with PNP received a single intervention with HCCP (N=282; 1-4 patches at baseline) or oral daily pregabalin (N=277; 150-600 mg, 8 weeks). At baseline (Day 0) and Week 8, patients completed the following PROs in addition to the regular pain assessments: Patient Global Impression of Change (PGIC Medical Outcomes Study Cognitive Functioning scale (MOS-Cog), Medical Outcomes Study Sleep scale (MOS-Sleep), Treatment Satisfaction Questionnaire for Medication (TSQM), and EuroQol 5-Dimensions 5-levels (EQ-5D-5L) utility index (EQ-UI) and visual analogue scale (EQ-VAS).

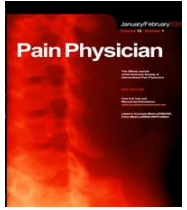
Eric Viel, Ph.D.

Mariëlle Eerdekens, MD

Prashanth Kandaswamy, MSc

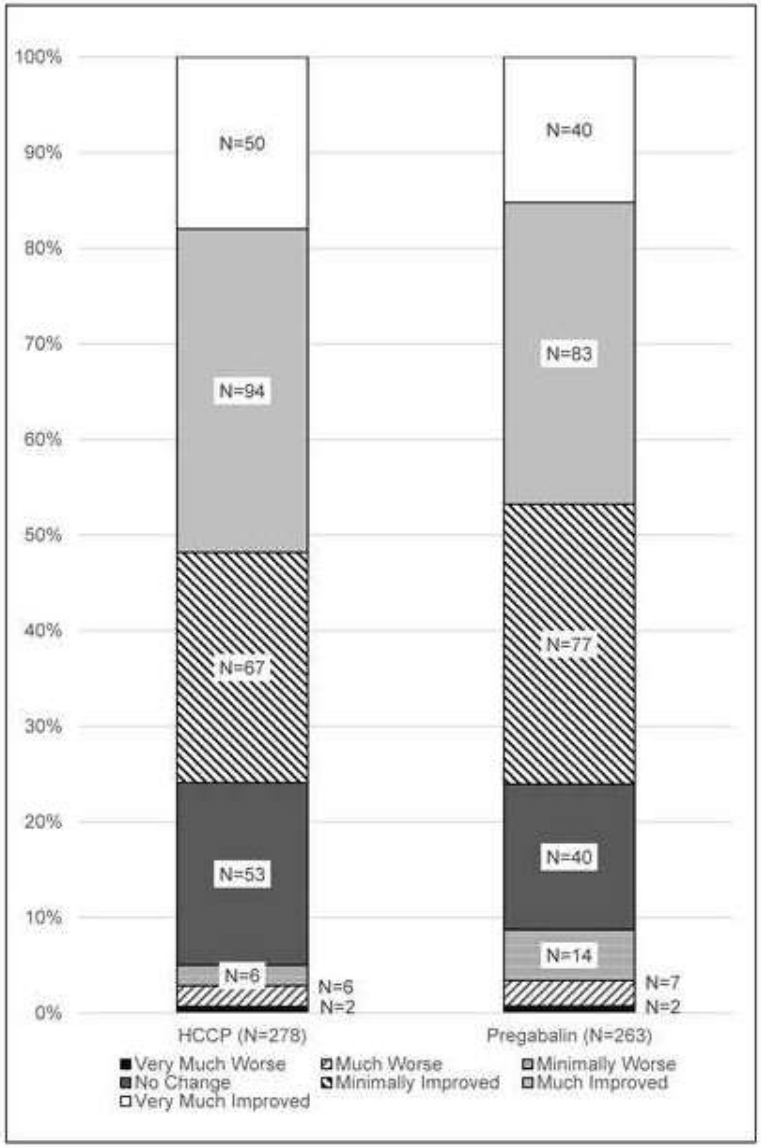


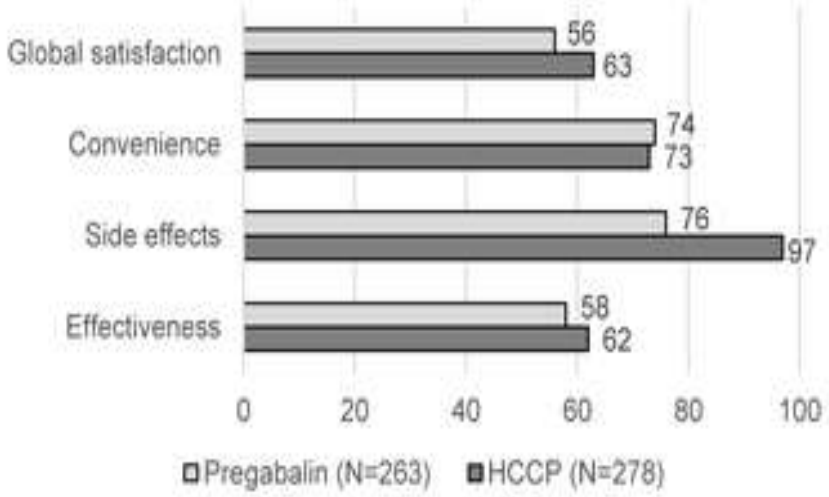
Nov. 2021



Results : At Week 8, 76% and 75.9% of patients on HCCP and pregabalin respectively, reported to be very much/much/minimally improved on the PGIC. HCCP application was associated with significant improvements from baseline vs pregabalin in MOS-Cog (mean difference: 4.28 [95% CI: 2.90-5.66], p<0.001), EQ-VAS (3.11 [0.30-5.92]; p=0.030), and TSQM global satisfaction (6.74 [2.29-11.20]; p=0.029), particularly the side-effects dimension (21.23 [17.55-24.94]; p<0.0001). No significant differences in improvements were noted for the MOS-Sleep, TSQM convenience, and EQ-UI.

Conclusions : Single intervention with HCCP showed benefits vs daily pregabalin at Week 8 on several PROs. While HCCP has been approved in the US for PNP treatment in diabetic patients, these observations provide information on how patients perceive the effects of distinct PNP treatments. They are complementing already existing knowledge on efficacy and safety of different treatment options with data on patient preferences and may help identifying the appropriate treatment option in dialogue with the patients and shared decision-making.





Clinical Therapeutics/Volume 39, Number 4, 2017

Capsaicin 8% Patch Versus Oral Neuropathic Pain Medications for the Treatment of Painful Diabetic Peripheral Neuropathy: A Systematic Literature Review and Network Meta-analysis

Floortje van Nooten, MSc[1,*]; Maarten Treur, MSc[2]; Krystallia Pantiri, MSc[2]; Malcolm Stoker, PhD[1]; and Mata Charokopou, MSc[2,†]

Implications: This NMA suggests that the efficacy observed with the capsaicin 8% patch is similar to that observed with oral agents (ie, pregabalin, duloxetine, gabapentin) in patients with PDPN. The oral agents were associated with a significantly elevated risk of somnolence, dizziness, fatigue, and discontinuation because of AEs compared with placebo. The capsaicin 8% patch was as effective as oral centrally acting agents in these patients with PDPN but offers systemic tolerability benefits. (*Clin Ther.* 2017;39:787–803) © 2017

Advances in neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet: Delivering a non-invasive direct nerve intervention

Jeffrey Fudin, Pharm.D
David M. Simpson, M.D
Eric Viel. M.D.. Ph.D.

September 12th , 2020 For U.S. healthcare professionals only as presented at the **Pain week** live Symposium on September 12th 2020, **Las Vegas**

Traiter dès que possible !

EJP
European Journal of Pain

ORIGINAL ARTICLE

Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study

C.G. Maihöfner[1], M.-L.S. Heskamp[2]

1 Fürth Hospital, Department of Neurology, University of Erlangen-Nuremberg, Germany
2 Medical Department, Astellas Pharma GmbH, Munich, Germany

Correspondence
Christian G. Maihöfner
E-mail: christian.maihoefner@uk-erlangen.de

Funding sources
This study was funded by Astellas Pharma GmbH, Munich, Germany. Study design, operational conduct, data analysis and manuscript preparation were undertaken by Astellas Pharma.

Conflicts of interest
The author Christian Maihöfner has received honoraria as consultant for Astellas, Bionorica and Mundipharma, and has participated in speakers bureaus of Allergan, Astellas, Grunenthal, Janssen and Pfizer. University Hospital Erlangen received financial support from Astellas Pharma to fund the investigation. The author Marie-Luise Heskamp was a salaried employee of Astellas Pharma at the time of the study.

Accepted for publication
10 September 2013

doi:10.1002/j.1532-2149.2013.00415.x

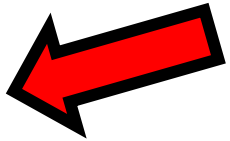
Abstract

Background: This study evaluates the impact of the duration of pre-existing peripheral neuropathic pain on the therapeutic response to the capsaicin 8% cutaneous patch.

Methods: The non-interventional QUEPP (QUTENZA – safety and effectiveness in peripheral neuropathic pain) study evaluated the effectiveness of Qutenza™ in 1044 non-diabetic patients with peripheral neuropathic pain, who received a single application. Follow-up visits were scheduled at weeks 1–2, 4, 8 and 12. A pre-defined co-analysis of changes in average pain intensity was performed based on the duration of pre-existing pain.

Results: In patients with pre-existing pain for <6 months, the mean relative change of the numeric pain rating scale score on days 7–14 to week 12 versus baseline was −36.6% [4.6 standard error of the mean (SEM); $n = 105$], −25.1% (1.9 SEM; $n = 311$) in patients with pain duration of 6 months to 2 years, −22.3% (1.6 SEM; $n = 391$) in patients with pain for >2–10 years, and −19.2% (2.6 SEM; $n = 99$) in patients with pain for >10 years. Thirty percent and 50% responder rates were 61.7% and 39.3% in patients with pre-existing pain for <6 months, 42.3% and 23.3% in patients with pain for 6 months to 2 years, 40.9% and 21.6% in patients with pain for >2–10 years, and 32.3% and 14.1% in patients with pain for >10 years.

Conclusions: The highest treatment response to the capsaicin 8% cutaneous patch was observed in patients with a history of pre-existing peripheral neuropathic pain of less than 6 months, suggesting that early initiation of topical treatment might be indicated.



de l'indication à la 1ère application : moins de 15 jours

Médecin ou I.D.E ?

Journal of Pain Research 18 July 2013

EXPERT OPINION

[1]Institute for Pain Medicine/Pain Practice, Wiesbaden, Germany; [2]Pain Medicine and Anaesthesia, The Christie National Health Service Foundation Trust, Manchester, UK; [3]Pain Therapy and Palliative Care Department, Medizinisches Zentrum Städteregion Aachen, Aachen, Germany

Is physician supervision of the capsaicin 8% patch administration procedure really necessary? An opinion from health care professionals

Kai-Uwe Kern[1] Janice England[2] Andrea Roth-Daniek[3] Till Wagner[3]

Neuropathic pain is difficult to treat and can have a severe effect on quality of life. The capsaicin 8% patch is a novel treatment option that directly targets the source of peripheral neuropathic pain. It can provide pain relief for up to 12 weeks in patients with peripheral neuropathic pain. Treatment with the capsaicin 8% patch follows a clearly defined procedure, and patch application must be carried out by a physician or a health care professional under the supervision of a physician. Nonetheless, in our experience, nurses often take the lead role in capsaicin 8% patch application without the involvement of a physician. We believe that the nurse's key role is of benefit to the patients, as he or she may be better placed, because of time constraints and patient relationships, to support the patient through the application procedure than a physician. Moreover, a number of frequently prescribed drugs, including botulinum toxin and infliximab, can be administered by health care professionals without the requirement for physician supervision. Here we argue that current guidance should be amended to remove the requirement for physician supervision during application of the capsaicin 8% patch.

Advancing Nursing Practice: Management of Neuropathic Pain With Capsaicin 8% Without Physician Supervision

Joanne O'Brien;Joseph Keaveny;Valerie Pollard;Linda Nugent

Clinical Nurse Specialist. 31(3):157–162, MAY/JUNE 2017

Purpose/Aims:

The purpose of this study was to examine the management of patient's neuropathic pain with capsaicin 8% in a nurse-led clinic when administered by 1 registered advanced nurse practitioner without physician supervision.

Design:

A longitudinal, single-group, descriptive research design was used to assess pain scores and quality of life 3 times over 3 months after treatment.

Methods:

Patients with a diagnosis of neuropathic pain were assessed and treated with capsaicin 8% by 1 advanced nurse practitioner with prescriptive authority in a nurse-led clinic. Pain scores were collected at baseline, and self-assessed pain, activity level, and quality of life were assessed at 1 week, 4 weeks, and 3 months after treatment. Twenty-four patients were recruited, and data were analyzed using Friedman's test. In post hoc analysis, Wilcoxon signed-rank test was used with Bonferroni correction.

Results:

Pain scores differed from pretreatment to posttreatment at each of the 3 time points, at rest ($\chi 23 = 20.54$, $P = .001$) and on movement ($\chi 23 = 23.644$, $P = .001$), and remained significant after Bonferroni correction. Overall, 62.5% (n = 15) of patients achieved at least a 30% reduction in self-reported pain at rest from pretreatment to 3 months, and 54% (n = 13) achieved the same reduction in pain on movement. Most improvements in patient's quality of life occurred between 1 and 4 weeks. Patient satisfaction was high, with 83% stating that they would be happy to have the treatment repeated.

Conclusion:

Single-dose capsaicin 8% decreased neuropathic pain after being administered in an outpatient setting by an experienced registered advanced nurse practitioner. Further multicenter research led by advanced nurse practitioners is needed to support high-quality, safe treatment of neuropathic pain with high-concentration capsaicin in nurse-led chronic pain clinics.

Capsaicin 179-mg cutaneous patch in the treatment of post-surgical neuropathic pain: a scoping review of current evidence and place in therapy

Roberto Casale

Expert Review of Neurotherapeutics
Volume 21, 2021 - Issue 10

REVIEW ARTICLE | VOLUME 60, ISSUE 5, P1047-1054.E1, NOVEMBER 01, 2020

High-Dose 8% Capsaicin Patch in Treatment of Chemotherapy-Induced Peripheral Neuropathy. A Systematic Review

Luis Cabezón-Gutiérrez, MD, PhD • Sara Custodio-Cabello, MD, PhD • Magda Palka-Kotlowska, MD
Parham Khosravi-Shahi, MD, PhD

JPSM JOURNAL OF PAIN AND SYMPTOM MANAGEMENT

Journal of Personalized Medicine

Luca Gregorio Giaccari, Caterina Aurilio, Francesco Coppolino, Maria Caterina Pace, Maria Beatrice Passavanti, Vincenzo Pota and Pasquale Sansone *

J. Pers. Med. 2021, 11, 960

Review

Capsaicin 8% Patch and Chronic Postsurgical Neuropathic Pain

The role of the capsaicin 8% patch in the treatment of painful diabetic peripheral neuropathy

Future Medicine

Yaowaree Leavell & David M Simpson

Published Online: 14 Feb 2022 | https://doi.org/10.2217/pmt-2021-0025

Current Opinion in
Supportive and Palliative Care

Capsaicin 8% patch Qutenza and other current treatments for neuropathic pain in chemotherapy-induced peripheral neuropathy (CIPN)

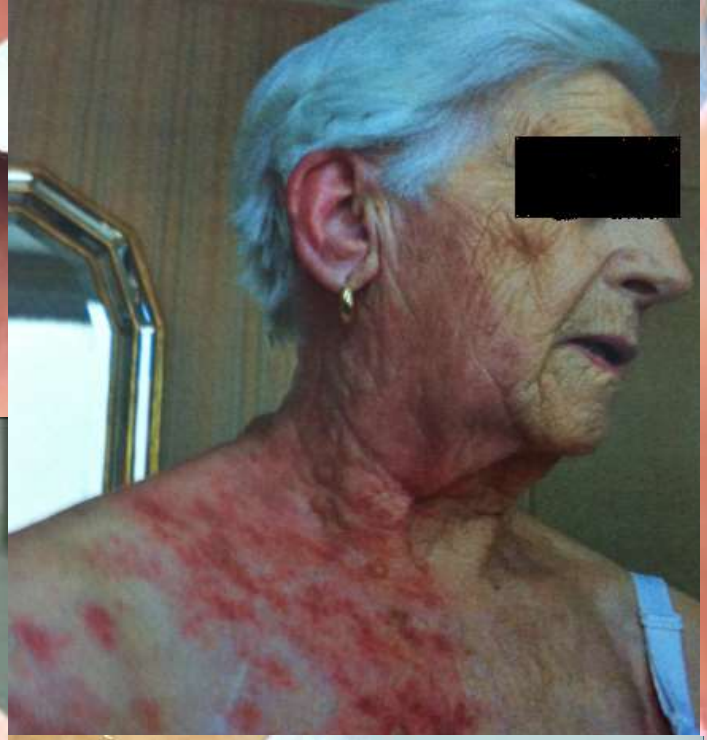
Privitera, Rosario; Anand, Praveen

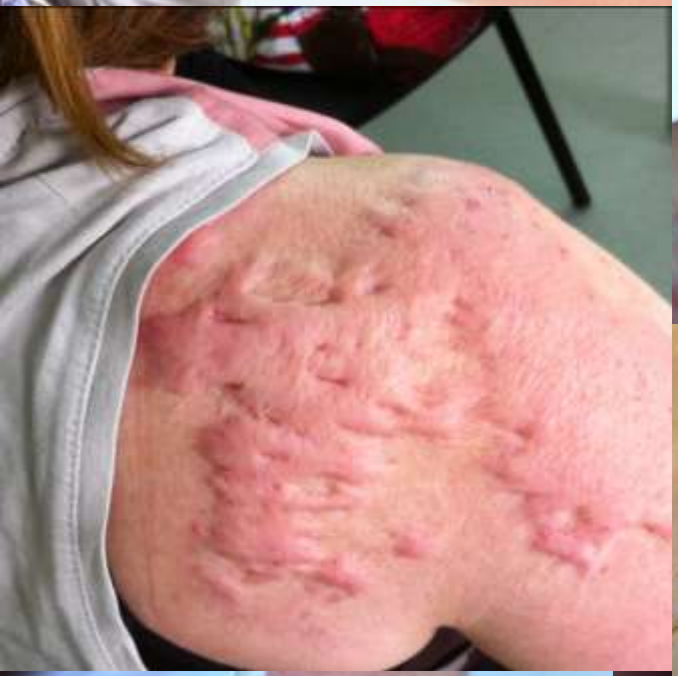
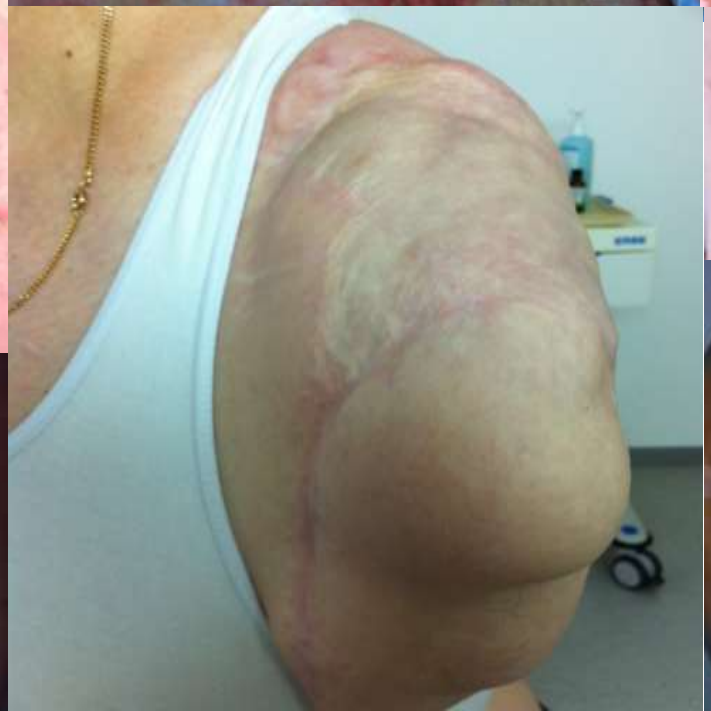
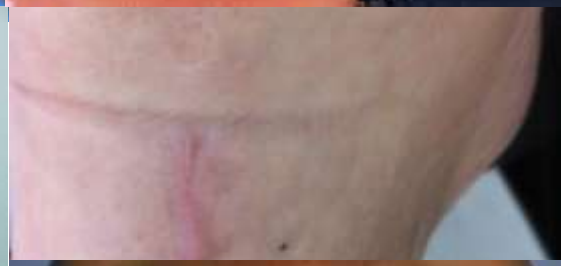
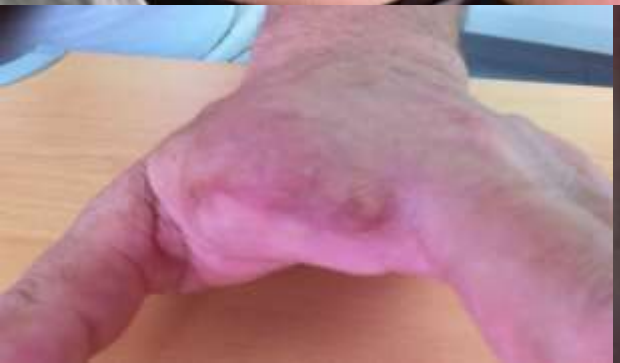
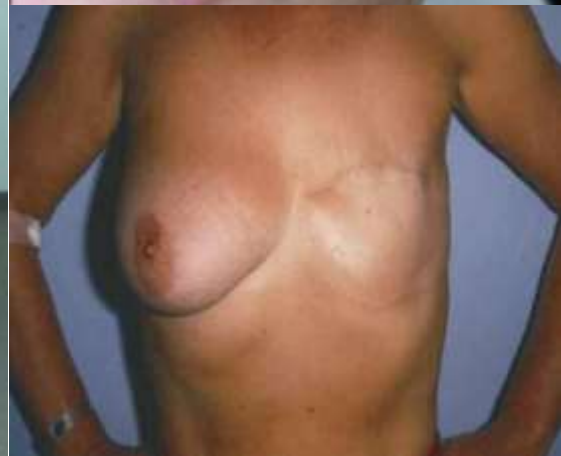
June 2021 - Volume 15 - Issue 2 - p 125-131

The Capsaicin 8% patch is now often a preferred a treatment option for localised neuropathic pain conditions, including the feet and hands in patients with CIPN. Capsaicin 8% patch can be repeated three-monthly, if needed, for a year. In addition to pain relief, it may have a disease-modifying effect.

Que retenir ?

- **L'efficacité de la capsaïcine dépend de la densité en fibres / en récepteurs TRPV1**
- **Celle-ci peut varier d'un patient à l'autre pour une même pathologie**
- **Le mode d'action principal est une défonctionnalisation des récepteurs TRPV1**
- **"*disease-modyfier*"**
- **Effet prolongé au-delà du retrait du patch**
- **Absence d'effets adverses systémiques**
- **Réduction intensité DNP et/ou surface**
- **Indications majeures ; cicatrices. NPZ/N.diabétique/ N.chimio-induite**
- **Peut être répété**
- **Peut être associé**

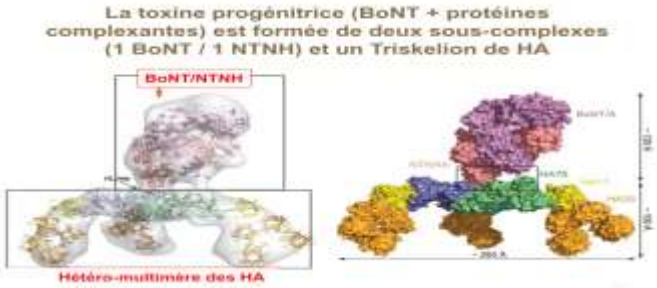






Toxine botulique A

toxins *Toxins* **2015**, *7*, 3127-3154; doi:10.3390/toxins7083127

Botulinum Toxin for Neuropathic Pain: A Review of the Literature

Hyun-Mi Oh and Myung Eun Chung



Deux siècles de recherche

1817. Paralysie flasque et dysautonomie par ingestion de boudin (*botulus*) (Kerner). Botulisme (Müller, **1870**).

1897. Identification de *Bacillus botulinus* (van Ermengen) > *C. botulinum.*
1919-2013. Différentes toxines et souches productrices…

1923-1949. Blocage libération d' ACh à la JNM et jonction nerf-glande

1946. Purification et cristallisation de la toxine A, 900 kDa (Lamanna).

1948. Activité hémagglutinante (Lamanna)

1966. La toxine est un complexe formé de la neurotoxine (150 kD) et de *protéines complexantes* (NAPs, dont HA hémagglutinantes) (DasGupta).

1981. Application de la toxine en opthtalmologie (Scott)

1984-1993. Mode d'action intracellulaire (Dolly, Poulain, Schiavo, Blasi)

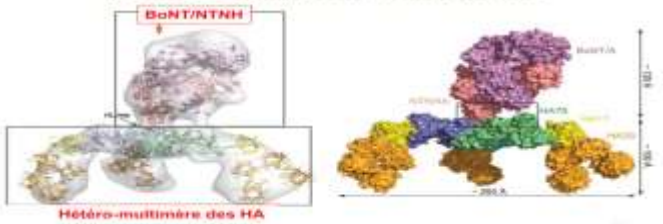
1992. Application de la toxine en esthétique (Carruthers et Carruthers).

1998. Structure 3D de la BoNT (Lacy et al)

1996-2006. Identification des récepteurs (Binz, Rummel…)

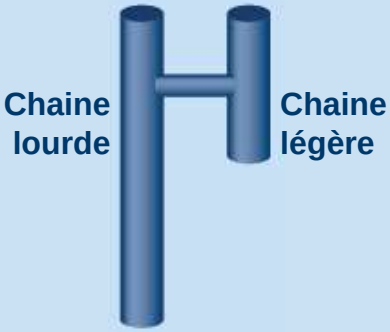
2014 — Structure 3D du complexe toxine + NAPS (Gu et al; Lee et al.)

La toxine progénitrice (BoNT + protéines complexantes) est formée de deux sous-complexes (1 BoNT / 1 NTNH) et un Triskelion de HA



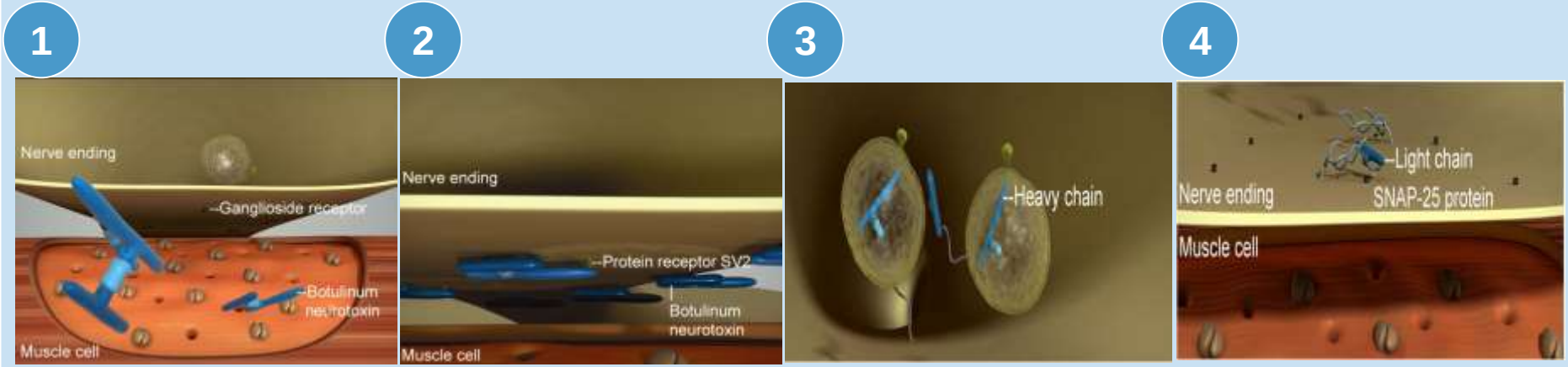
Toxine botulinique de type A
Mécanisme d'action en 4 étapes

Toxine botunique de type A

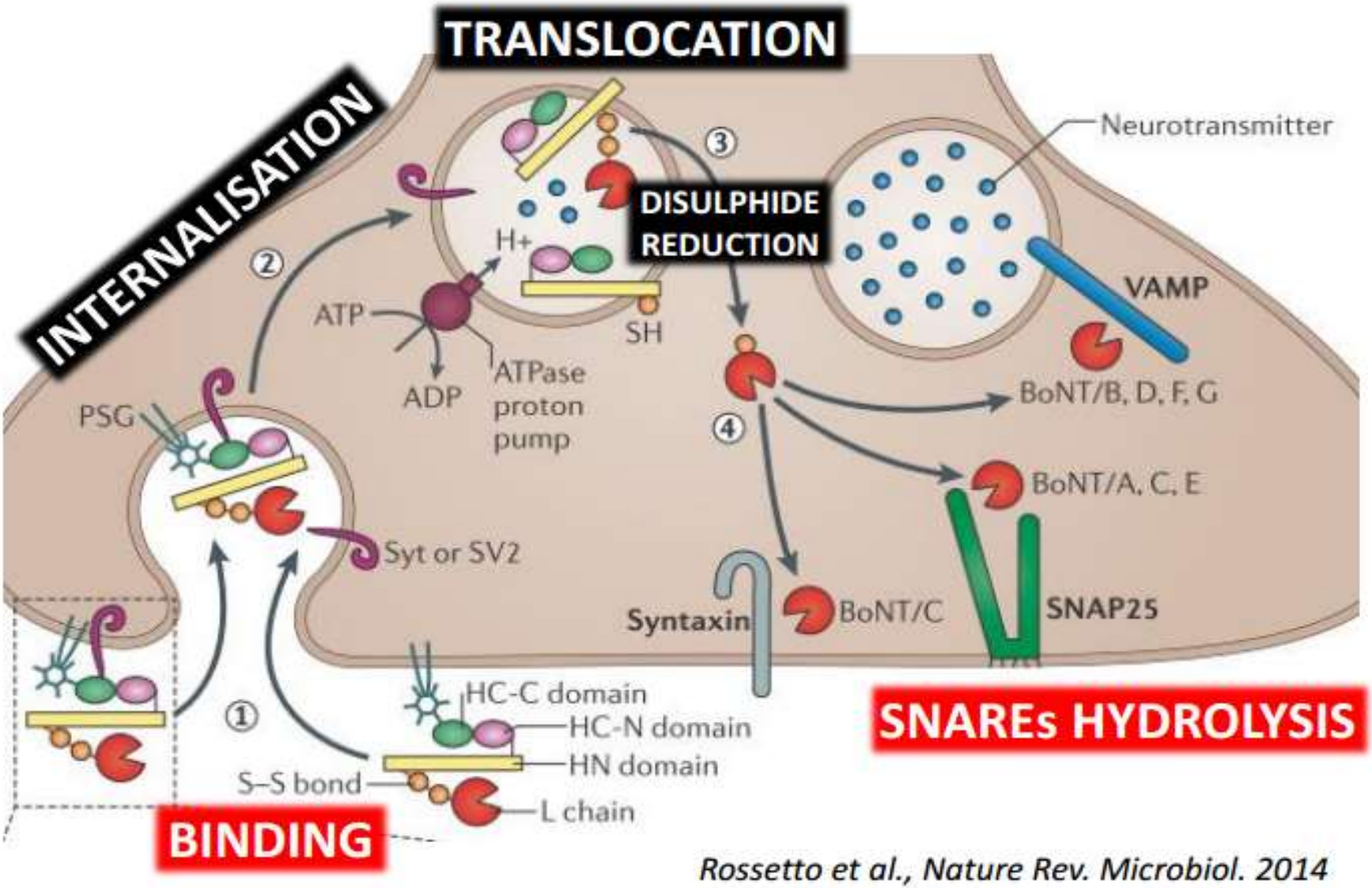


Le mécanisme d'action comporte 4 étapes :

1. Liaison spécifique de la chaine lourde aux recepteurs de la terminaison nerveuse présynaptique
2. Internalisation de la neurotoxine
3. Translocation de la chaine légère dans le cytosol
4. Clivage de la SNAP-25 par la chaine légère, empêchant la libération de l'acétylcholine



Photos : Medical Science Unit Germany in collaboration with Professor Bilgalke



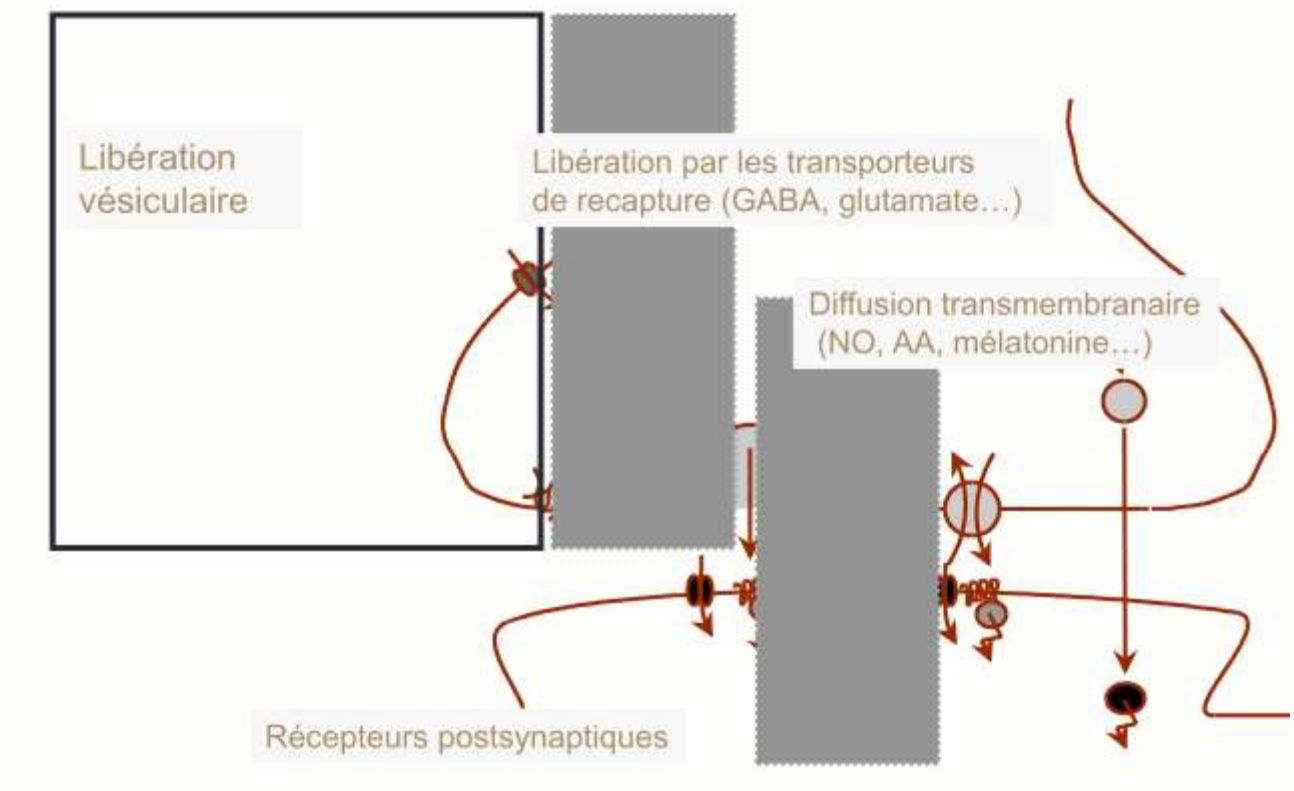
Rossetto et al., Nature Rev. Microbiol. 2014

Comme les toxines attaquent les complexes SNARE,
Elles bloquent l'exocytose d'autres neuromédiateurs …

Neurotransmitter	Model system	Ref.
ACh	NMJ Torpedo electric organ Aplysia CNS	Burgen et al., 1949 Dunant et al 1987 Poulain et al., 1988
Glutamate,	Brain synaptosomes Hindpaw /Mass spectrometry Cultured granule neurons	Sanchez Prieto et al. 1987; Cui et al. 2004, Foran et al., 2003
Aspartate	Brain synaptosomes	McMahon et al., 1992
GABA	Brain synaptosomes	Ashton et Dolly, 1988; McMahon et al., 1992
Glycine	Primary culltures of spinal chord neurones	Neales et al., 1999
DA, A, NA	Brain synaptosomes	Maisey et al., 1988; Ashton et Dolly, 1988;
5-HT	Brain synaptosomes	Najib et al., 1999
ATP (co-release with ACh)	Torpedo synaptosomes	Marsal et al., 1990
CGRP	NMJ (accumulation) Trigeminal (V) nerve endings	Hassan et al., 1994; Meunier et al., 1996 Durham et al., 2004
Substance P	Neurones DRG	Purkiss et al., 1997; Welch et al., 2000

Reviewed by **Jover et al., *SFET-ebook*, 2009; Popoff & Poulain, *Toxins*, 2010, *2*:683-737**

Parce qu'elles attaquent seulement les SNAREs, les BoNTs bloquent spécifiquement l'exocytose vésiculaire



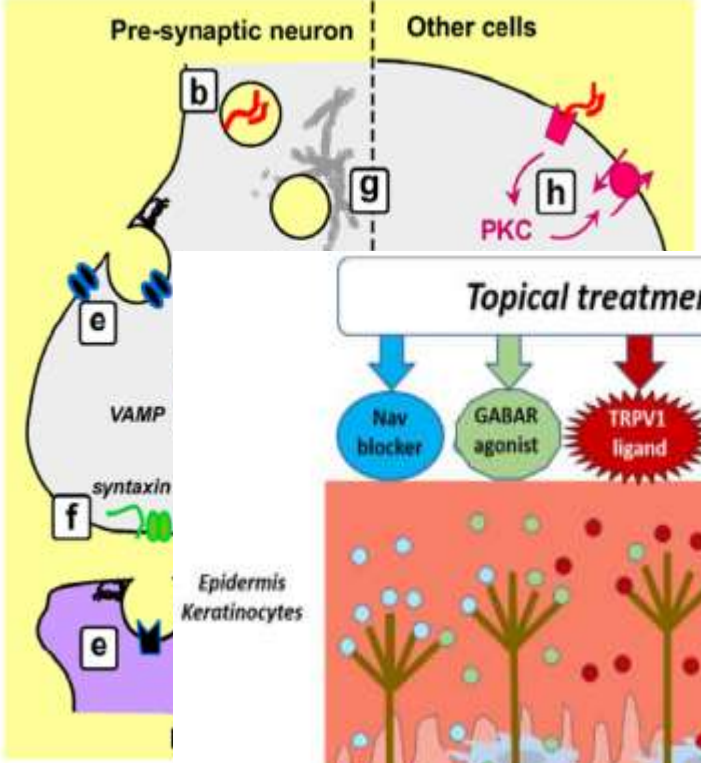
BoNT → Clivage de SNAP 25 en syntaxine et synaptobrevine

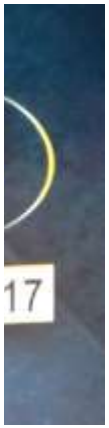
Ainsi que le transport axonal de certains récepteurs…

Receptor	BoNT effect	Model system / Refs
GluR (AMPA-R	Decrease in LTP amplitude Decrease AMPA-R insertion	LTP in CA1 Lledo et al., 1998; Cerebellar NO-induced PF-LTP, Kakegawa and Yuzaki, 2005; L-type channel driven insertion of AMPA-R in mouse CA1; Baxter and Willie, 2006
NMDA-R (NR1)	Decrease insertion	mGluR1 driven insertion of NR1in Xenopus oocyte membrane Lan et al, 2001.
Gephyrin (Glycine-Receptors)	Decrease in immunoreactivity	2 months post injection in Cat abducens motoneurons Moreno-Lopez et al, 1998,
α7-nAChR	Reduced activity-driven trafficking	Somatic spines in cultured chick ciliary ganglion. Liu et al, 2005
H^+-ATPase	Reduced trafficking	SNAP-23 dependent trafficking of H+-ATPase in cultured **inner medullary collecting duct cells** of the rat (Banerjee et al., 2001.
Transferrin-R	Reduced recycling	Knight 2002

La toxine botulique peut agir sur l'exocytose de nombreux neurotransmetteurs au niveau de toute cellule contenant le complexe SNARE et les récepteurs correspondants

- Acétylcholine, AAE (GLU), glycine, sérotonine





Long
Neu
Flavia A

Botu
Axor
Laura R
Ornella

PAIN 2014

Botulinum toxin type A selectivity for certain types of pain is associated with capsaicin-sensitive neurons

Ivica Matak [a], Ornella Rossetto [b], Zdravko Lacković [a,*]

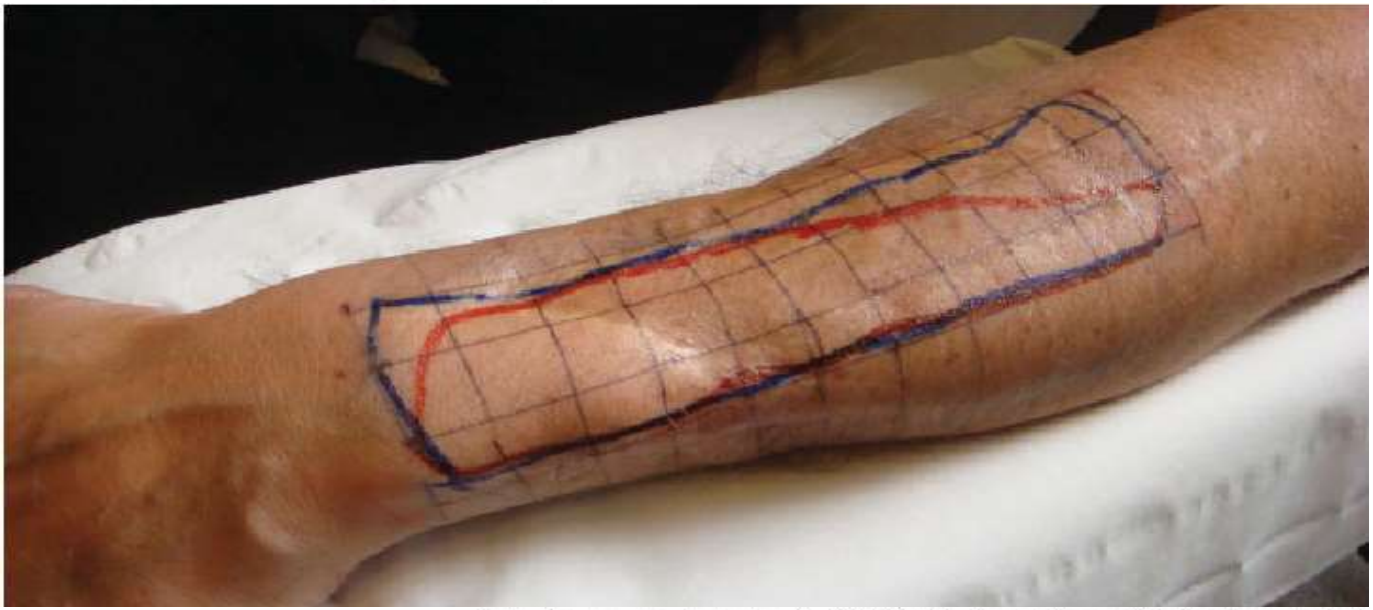
d

Botulinum Toxin Type A Induces Direct Analgesic Effects in Chronic Neuropathic Pain

Ann Neurol 2008;64:274–284

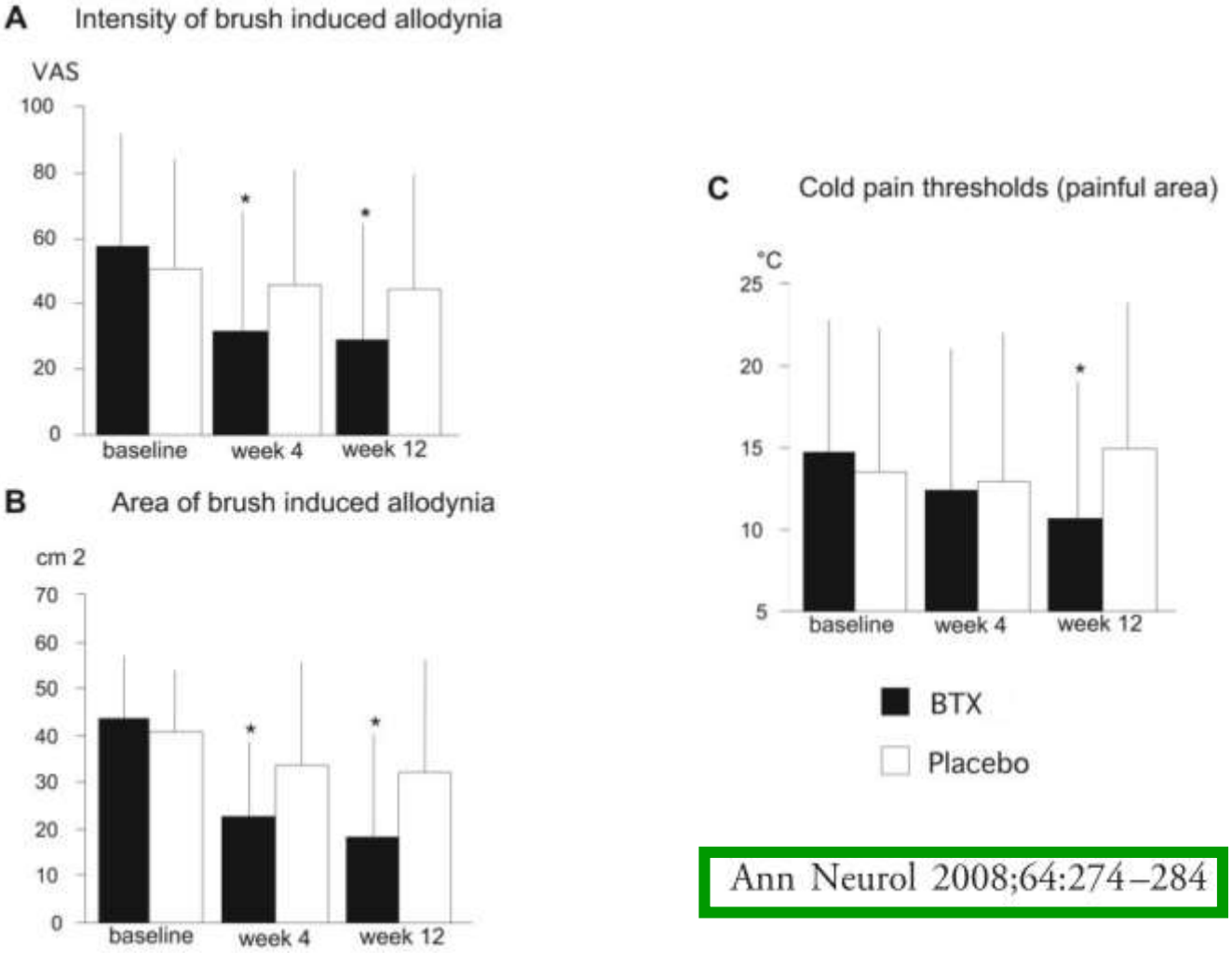
Danièle Ranoux, Nadine Attal, Francoise Morain, D. Bouhassira

Botulinum toxin type A (BTX-A) has been reported to have analgesic effects independent of its action on muscle tone, possibly by acting on neurogenic inflammation. Such a mechanism may be involved in peripheral neuropathic pain.



botulinum toxin type A (BTX-A) intradermal injection technique for the painful area in one male patient with posttraumatic radial nerve lesion just before BTX-A injection. Intradermal injections were performed using equidistant grid lines 1.5cm apart (marked in black) aiming to cover the area of maximal spontaneous pain (in blue) and the whole area of allodynia (in red).

Toxines botuliques / douleurs chroniques



Ann Neurol 2008;64:274–284

Interpretation: These results indicate for the first time that BTX-A may induce direct analgesic effects in patients with chronic neuropathic pain independent of its effects on muscle tone and suggest novel indications for BTX-A in analgesia.

Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial

Nadine Attal, Daniel C de Andrade, Frédéric Adam, Danièle Ranoux, Manoel J Teixeira, Ricardo Galhardoni, Irina Raicher, Nurcan Üçeyler, Claudia Sommer, Didier Bouhassira

Lancet Neurol 2016; 15: 555–65

Summary

Background Data from previous studies suggest that botulinum toxin A has analgesic effects against peripheral neuropathic pain, but the quality of the evidence is low. We aimed to assess the safety and efficacy of repeated administrations of botulinum toxin A in patients with neuropathic pain.

Methods We did a randomised, double-blind, placebo-controlled trial at two outpatient clinics in France (Clinical Pain Centre, Ambroise Paré Hospital, APHP, Boulogne-Billancourt, and Neurological Centre, Hôpital Dupuytren, Limoges) and one in Brazil (Neurological Department, Hospital das Clínicas da FMUSP, São Paulo). Patients aged 18–85 years with peripheral neuropathic pain were randomly assigned (1:1) by block randomisation, according to a centralised schedule, to receive two subcutaneous administrations of botulinum toxin A (up to 300 units) or placebo, 12 weeks apart. All patients and investigators were masked to treatment assignment. The primary outcome was the efficacy of botulinum toxin A versus placebo, measured as the change from baseline in self-reported mean weekly pain intensity over the course of 24 weeks from the first administration. The primary efficacy analysis was a mixed-model repeated-measures analysis in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01251211.

Findings Between Oct 2, 2010, and Aug 2, 2013, 152 patients were enrolled, of whom 68 were randomly assigned (34 per group), and 66 (37 [56%] men) were included in the primary analysis (34 in the botulinum toxin A group and 32 in the placebo group). Botulinum toxin A reduced pain intensity over 24 weeks compared with placebo (adjusted effect estimate –0·77, 95% CI –0·95 to –0·59; p<0·0001). Pain on injection was the only adverse effect reported, and occurred in 19 (56%) participants in the botulinum toxin A group and 17 (53%) of those in the placebo group (p=1·0). Severe pain was experienced by ten (29%) participants in the botulinum toxin A group and 11 (34%) in the placebo group (p=0·8).

Interpretation Two administrations of botulinum toxin A, each of which comprised several injections, have a sustained analgesic effect against peripheral neuropathic pain. Several factors, such as the presence of allodynia and a limited thermal deficit, may be useful in predicting treatment response and should be investigated further.

	Botulinum toxin A (n=34)	Placebo (n=32)
Age (years)	51·6 (16·7)	52·3 (15·8)
Sex		
Male	17 (50%)	20 (63%)
Female	17 (50%)	12 (38%)
Pain duration (years)	5·1 (4·7)	6·3 (7·4)
Mean pain intensity*	6·5 (1·6)	6·4 (1·6)
Cause of pain		
Post-traumatic or postsurgical†	25 (74%)	21 (66%)
Polyneuropathy‡	5 (15%)	9 (28%)
Postherpetic neuralgia	4 (12%)	2 (6%)
Area of maximum pain		
Hand or forearm	14 (41%)	16 (50%)
Foot or ankle	12 (35%)	13 (41%)
Thorax or abdomen	6 (18%)	3 (9%)
Shoulder	2 (6%)	0
Concomitant analgesics		
Antidepressants	25 (74%)	28 (88%)
Gabapentin or pregabalin	9 (26%)	11 (34%)
Opioids	17 (50%)	14 (44%)
NSAIDs or paracetamol	12 (35%)	17 (53%)
Other antiepileptics§	6 (18%)	6 (19%)

Data are mean (SD) or number (%). Some percentages do not add up to 100 because of rounding. NSAID=non-steroidal anti-inflammatory drug. *On the numerical rating scale (range 0–10) of the Brief Pain Inventory from pain diaries at baseline. †25 (38%) participants had post-traumatic nerve lesions (14 in the botulinum toxin A group and 11 in the placebo group) and 21 (32%) had postsurgical nerve lesions (ten and 11). Post-traumatic nerve lesions corresponded to work or sports accidents (eg, crush, luxation, or fracture), but not to amputations or scars. ‡Causes were chronic inflammatory demyelinating neuropathy in five patients (two in the botulinum toxin A group and three in the placebo group), diabetes in two (both in the placebo group), idiopathic small fibre neuropathy in four (two in each group), vasculitis in two (one in each group), and leprosy in one (botulinum toxin A group). §Clonazepam, carbamazepine, and lamotrigine.

Table 1: **Demographics and baseline clinical characteristics**

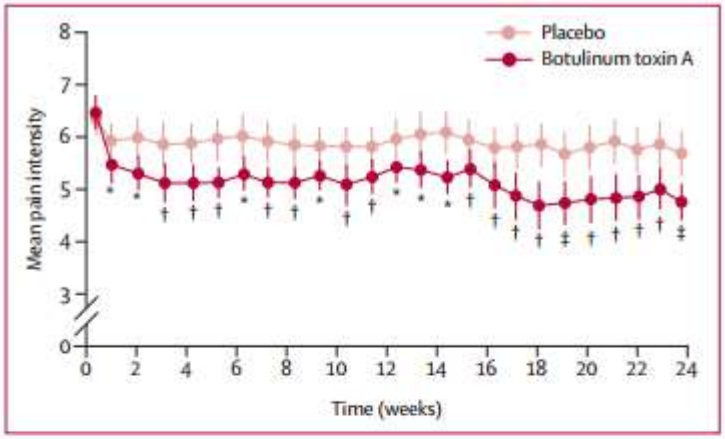


Figure 2: **Effects of botulinum toxin A and placebo on the primary endpoint**
Bars are SE. p values are for the difference between botulinum toxin A and placebo at each timepoint. *p<0·05. †p<0·01. ‡p<0·001.

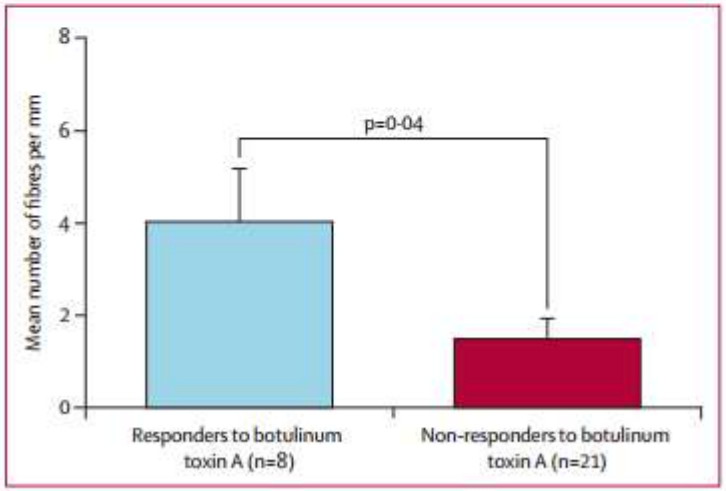


Figure 3: **Intra-epidermal nerve fibre density at baseline**
Bars are SD.

In participants who received at least one administration of botulinum toxin A (n=34), the efficacy of the treatment on mean pain intensity over 24 weeks was greater in participants with allodynia (based on the NPSI) at baseline (n=15) than in those without allodynia (n=19; adjusted effect estimate 0·56 [SE 0·14]; p=0·0003). We noted similar findings when allodynia was defined on the basis of QST (n=59 [29 with allodynia and 30 without]; adjusted effect estimate 0·59 [SE 0·14]; p=0·0002). The response to botulinum toxin A at 24 weeks (≥50% pain relief) was also predicted by the severity of brush-induced allodynia (odds ratio 4·6, 95% CI 1·5–13·7; p=0·007) and pressure hyperalgesia (3·5, 1·03–12·2; p=0·04) on QST. Finally, we noted significant positive or inverse correlations between the efficacy of botulinum toxin A at 24 weeks and baseline warm detection thresholds (Rho –0·49; p=0·03), cold detection thresholds (Rho 0·46; p=0·02), and mechanical pain thresholds (Rho –0·42; p=0·02) on the painful side, showing that less thermal deficits and stronger mechanical allodynia were associated with greater efficacy of botulinum toxin A. No such relations were noted in the placebo group.

Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP):

Fightin … oxin A

Back in th… incidentally f… known spasr… ndreas Binder

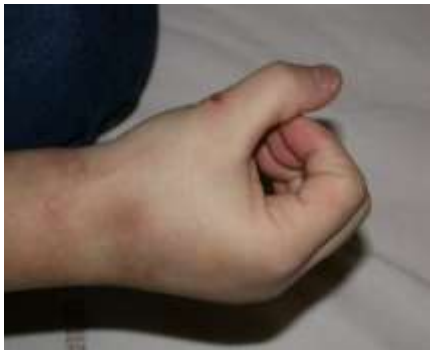
*Calculated as the inverse of the absolute difference between the proportion of responders in the active and placebo treatment groups (based on a 50% decrease in pain). †Risk of bias, inconsistency, and imprecision were high.

Table 5: Treatments for peripheral neuropathic pain and quality of the evidence

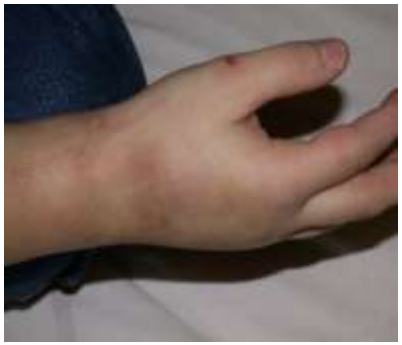
toxins **Domenico Intiso , Mario Basciani , Andrea Santamato , Marta Intiso and Filomena Di Rienzo**

Botulinum Toxin Type A for the Treatment of Neuropathic Pain in Neuro-Rehabilitation

Toxins **2015**, *7*, 2454-2480;



Pain is a natural protective mechanism and has a warning function signaling imminent or actual tissue damage. Neuropathic pain (NP) results from a dysfunction and derangement in the transmission and signal processing along the nervous system and it is a recognized disease in itself. The prevalence of NP is estimated to be between 6.9% and 10% in the general population. This condition can complicate the recovery from stroke, multiple sclerosis, spinal cord lesions, and several neuropathies promoting persistent disability and poor quality of life.



BTX-A has an effect in relief pain that may characterize less common neurological disorders including post-traumatic neuralgia, phantom limb, and complex regional pain syndrome with focal dystonia. The use of BTX-A could represent a novel therapeutic strategy in caring for neuropathic pain whenever common pharmacological tools have been ineffective.

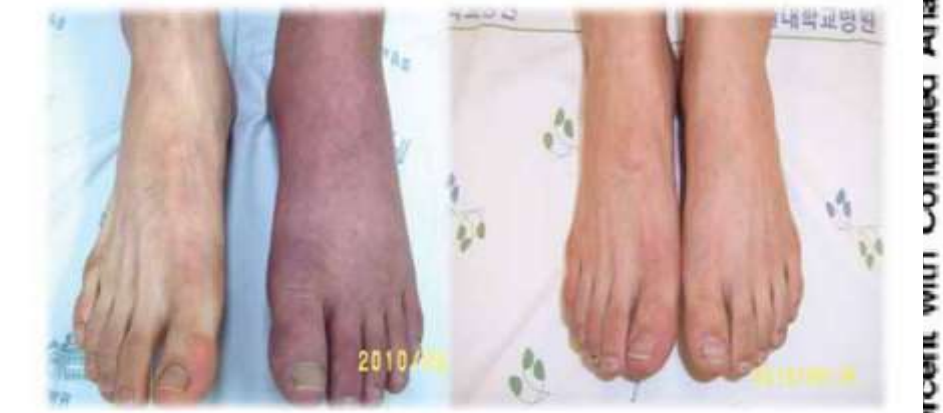
Sympathetic Block with Botulinum Toxin to Treat Complex Regional Pain Syndrome

Ann Neurol. 2009 March ; 65(3): 348–351

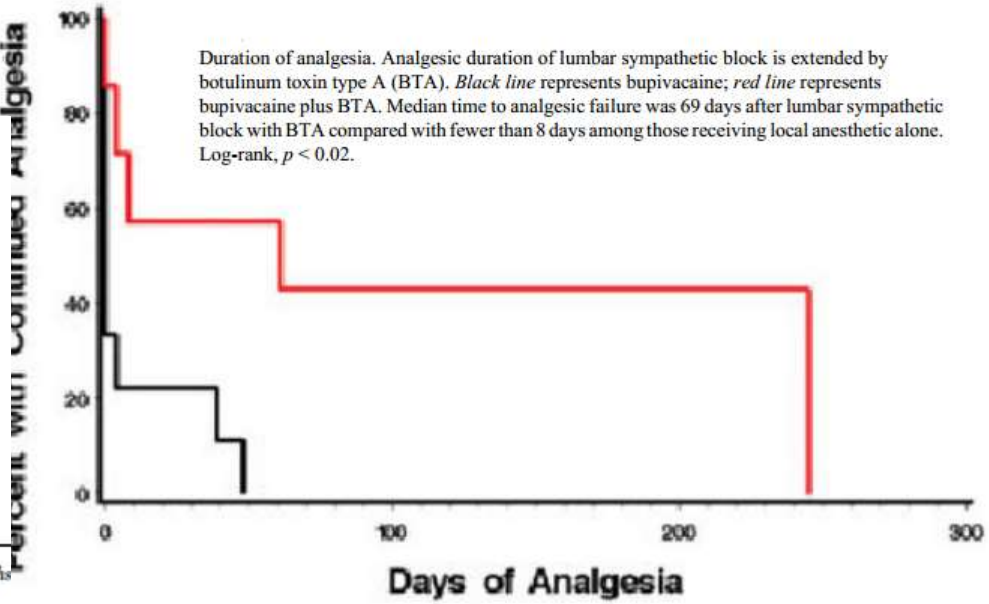
Ian Carroll, J. David Clark and **Sean Mackey**

Complex regional pain syndrome is a refractory pain condition with few tested therapies. We hypothesized that botulinum toxin A (BTA) would prolong analgesia after sympathetic blocks in patients with complex regional pain syndrome. We compared the duration of standard lumbar sympathetic block (LSB) with bupivacaine to LSB with bupivacaine and BTA in nine patients with refractory complex regional pain syndrome. Median time to analgesic failure was 71 (95% confidence interval, 12–253) days after LSB with BTA compared with fewer than 10 days (95% confidence interval, 0–12) after standard LSB (log-rank, $p < 0.02$). BTA profoundly prolonged the analgesia from sympathetic block in this preliminary study.

75 units BTA



Case 1 Skin color change before the lumbar sympathetic block (LSB) with botulinum toxin type B (BTX-B). Two months after LSB with BTX-B. Skin color and turgor normalized.



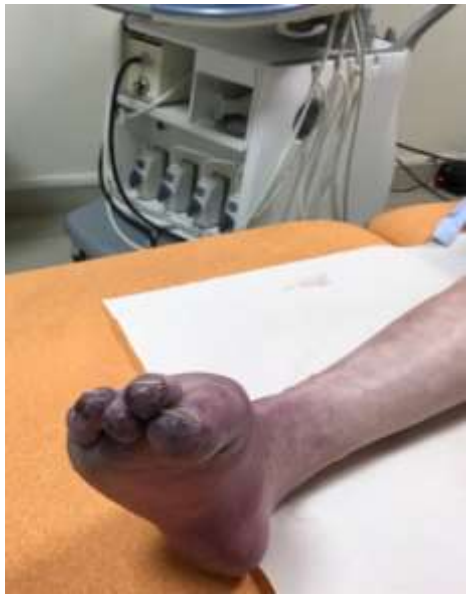
Duration of analgesia. Analgesic duration of lumbar sympathetic block is extended by botulinum toxin type A (BTA). *Black line* represents bupivacaine; *red line* represents bupivacaine plus BTA. Median time to analgesic failure was 69 days after lumbar sympathetic block with BTA compared with fewer than 8 days among those receiving local anesthetic alone. Log-rank, $p < 0.02$.

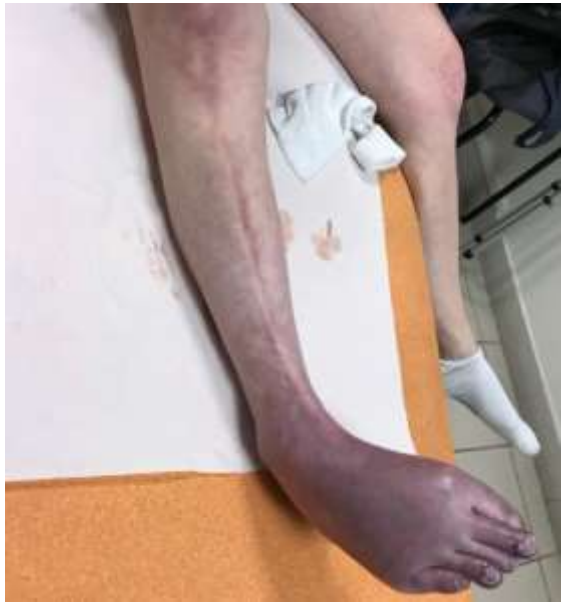
Responsiveness to botulinum toxin type A in muscles of complex regional pain patients with tonic dystonia

J Neural Transm (2014) 121:761–767

Johanna Schilder · J. Gert van Dijk · Dirk Dressler · Johannes Koelman · Johan Marinus · Jacobus van Hilten

Tonic dystonia of the limbs in complex regional pain syndrome (CRPS) is associated with considerable disability. Treatment options are scarce. Botulinum toxin (BoNT) is sometimes used, but the effect is often said to be disappointing. However, this notion stems from case reports and clinicians' opinions but has never been formally studied. We therefore investigated responsiveness to BoNT in CRPS patients with tonic dystonia. We injected the extensor digitorum brevis (EDB) muscle with BoNT-A in 17 patients with CRPS and tonic dystonia to compare the response between affected and unaffected legs. We also investigated the right legs of 17 healthy controls. Responsiveness was defined as a decrease of the amplitude of the compound muscle action potential (CMAP) of >20 % from baseline 2 weeks after BoNT-A injection. We controlled for a temperature effect on BoNT efficacy by measuring skin temperature hourly directly above the EDB muscle in the first 2 weeks. CMAP amplitude decreased >20 % after injection on the affected side in 16 of 17 CRPS patients, similar to the response in unaffected legs (12/13) or legs of controls (17/17). The degree of CMAP reduction was significantly smaller in patients than in controls (56.0 ± 22.3 vs. 70.6 ± 14.6 %; $p = 0.031$). This may be due to a lower physical activity level and a greater difficulty to localize the EDB muscle properly in affected legs. The decrease in CMAP amplitude was not related to skin temperature. Contrary to the prevailing opinion, BoNT-A has a normal, although perhaps slightly lower efficacy in CRPS patients with dystonia.





Pain Medicine

Pain Medicine 2014; 15: 292–305

Phantom Limb Pain: Systematic Neuroanatomical-Based Review of Pharmacologic Treatment

Zachary McCormick, MD, George Chang-Chien, DO, Benjamin Marshall, DO, Mark Huang, MD, and R. Norman Harden, MD

Results. We found level 2 evidence for gabapentin, both oral (PO) and intravenous (IV) morphine, tramadol, intramuscular (IM) botulinum toxin, IV and epidural Ketamine, level 3 evidence for amitriptyline, dextromethorphan, topiramate, IV calcitonin, PO memantine, continuous perineural catheter analgesia with ropivacaine, and level 4 evidence for methadone, intrathecal (IT) buprenorphine, IT and epidural fentanyl, duloxetine, fluoxetine, mirtazapine, clonazepam, milnacipran, capsaicin, and pregabalin.

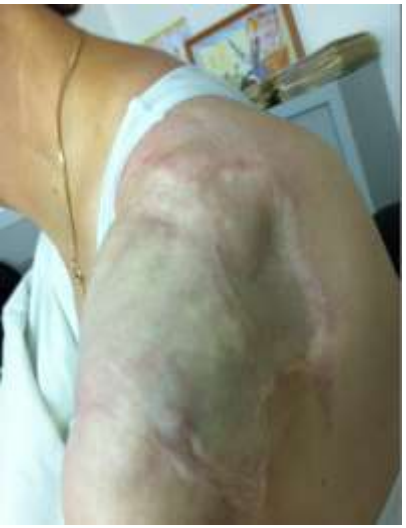
The peripheral afferent theory of PLP centers around the neuroma as a generator of pain and potentially a driver of secondary central changes. Neuromas form at the cut end of the nerves in the residual limb. They generate ectopic afferent impulses that may be perceived as pain by the brain.

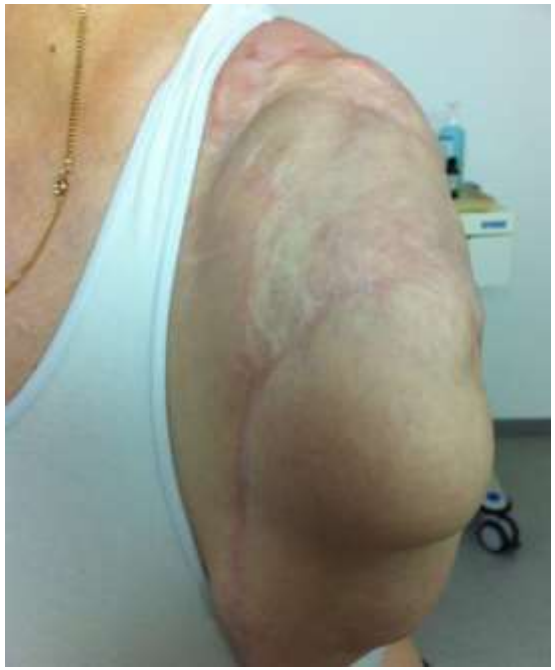
Botulism toxin injection is commonplace in the treatment of pain syndromes related to tonic muscle spasm and has recently been appreciated to have analgesic properties independent of its effect on neuromuscular transmission Though initial level 4 evidence demonstrated some promise in the treatment of PLP with local botulism toxin injection [71–73], a recent randomized, double-blinded pilot study of 14 patients with chronic PLP found no improvement in pain intensity up to 6 months following local injection.

A Prospective Randomized Double-blinded Pilot Study to Examine the Effect of Botulinum Toxin Type A Injection Versus Lidocaine/Depomedrol Injection on Residual and Phantom Limb Pain:

Clin J Pain. 2012 February ; 28(2): . doi:10.1097/AJP.0b013e3182264fe9.

Hong Wu, Rizwana Sultana, Kerrey Barton Taylor and **Aniko Szabo**





Pain Medicine Volume 10 • Number 2 • 2009

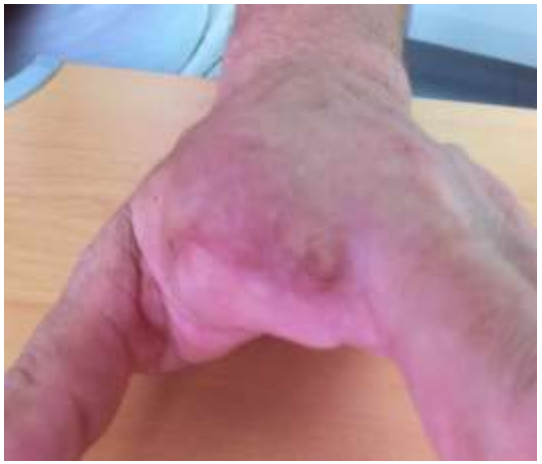
Treatment of Phantom Limb Pain with Botulinum Toxin Type A

Lingjing Jin, Katja Kollewe, Klaus Krampfl, Reinhard Dengler, Bahram Mohammadi

Methods. Three patients who had previously undergone amputation of their leg due to accident (N = 2) or injury by a landmine (N = 1) were treated with BoNT-A (Dysport®). We injected a total dose of up to 500 units (U) BoNT-A under EMG-control. Global clinical improvement was based on a 0–3 scale (0 = no effect; 3 = marked improvement) and on a questionnaire rating pain intensity (based on the visual analog scale), intake of pain medication and phantom limb sensations.

Results. All three patients evaluated the clinical global improvement with 3 (marked improvement). The pain intensity and pain medication was reduced significantly in all three cases. No side effects were reported. The duration of response lasted up to 11 weeks.

Discussion. These three successfully treated phantom and stump pain patients show that therapy with BoNT-A may be worth studying as an effective and safe treatment option for this kind of pain.



Intradermal Botulinum Toxin Type A Injection Effectively Reduces Residual Limb Hyperhidrosis in Amputees: A Case Series

Arch Phys Med Rehabil 2008;89:1407-9

Alexandra Charrow, Marc DiFazio, Leslie Foster, Paul F. Pasquina, Jack W. Tsao

Effect of BTX-A Treatment on Residual Limb Hyperhidrosis, Prosthesis Fit and Function, and Pain Levels

Clinical Measure	Before BTX-A Treatment	After BTX-A Treatment	*P*
Degree of hyperhidrosis	7.1±1.9	3.5±1.4	.001
Interference of prosthesis function by hyperhidrosis	7.1±2.1	2.9±1.7	.008
Interference of prosthesis fit by hyperhidrosis	7.2±2.1	2.8±2.3	.028
Severity of phantom limb pain	3.5±2.6	4.0±2.2	.39
Severity of residual limb pain	4.2±2.8	3.8±2.9	.89

NOTE. Values are mean ± SD.

Main Outcome Measure: A 10-cm continuous Likert visual analog scale was used to assess residual limb sweating and pain and prosthesis fit and function before and 3 weeks after BTX-A injections.

Results: Patients reported a significant reduction in sweating and improvement in prosthesis fit and function after treatment. However, residual limb and phantom pain were unaffected by treatment.

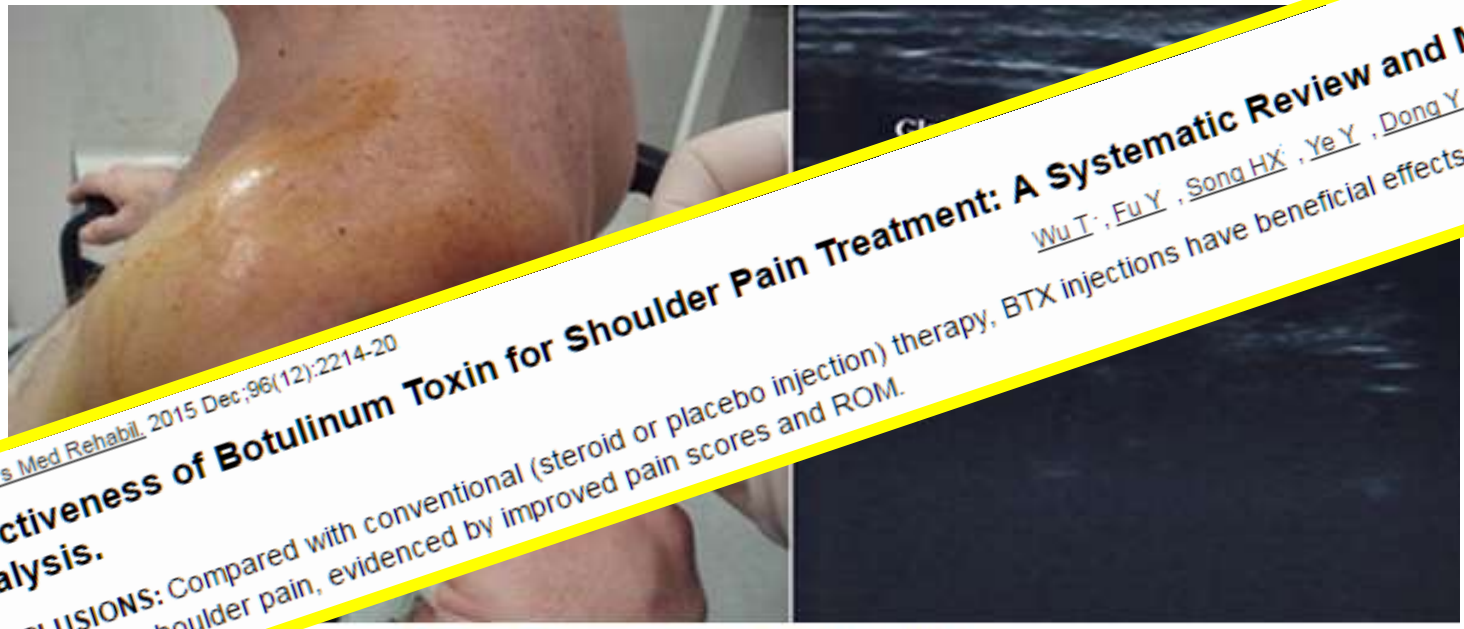
Conclusions: BTX-A may be an effective treatment for residual limb hyperhidrosis, resulting in subjective improvement in prosthesis fit and functioning. BTX-A should be considered as a method to manage excessive sweating in the residual limb of traumatic amputees.

Toxine intra-articulaire

Efficacy of Intra-Articular Injection of Botulinum Toxin Type A in Refractory Hemiplegic Shoulder Pain

Alberto Castiglione Sergio Bagnato Cristina Boccagni Marcello C. Romano Giuseppe Galardi

To evaluate the efficacy of intra-articular injection of botulinum toxin type A (BTX-A) in relieving hemiplegic shoulder pain (HSP).



Arch Phys Med Rehabil. 2015 Dec;96(12):2214-20

Effectiveness of Botulinum Toxin for Shoulder Pain Treatment: A Systematic Review and Meta-Analysis.

Wu T , Fu Y , Song HX , Ye Y , Dong Y , Li JH

CONCLUSIONS: Compared with conventional (steroid or placebo injection) therapy, BTX injections have beneficial effects for adult patients with shoulder pain, evidenced by improved pain scores and ROM.

Archives of Physical Medicine and Rehabilitation
Volume 92, Issue 7, July 2011, Pages 1034-1037

We found a strong correlation between intra-articular BTX-A injection and pain relief in patients with HSP. This result could provide the rationale for blind randomized controlled trials designed to better evaluate the safety and efficacy of intra-articular BTX-A injection in patients with refractory HSP.

Toxine intra-articulaire

Authors	Study design/duration	Indication	Age (mean ± SD)	Patients (n/sex)	Primary evaluation criterion	Results/Efficacy	Jadad/Oxford Quality score
Andrea J. Boon et al. [26]	RCT double blind 6 months	Knee OA II/III	62 years	$n = 60$ (35 F/25 M) 100 U BTX-A ($n = 20$) 200 U BTX-A ($n = 20$) 40 mg MPA ($n = 20$)	VAS pain score at 4 and 8 weeks	P^*: significant decreases in the WOMAC total score and pain subscore in all three groups	4/5
Chen-Liang et al., [27]	Open-label clinical trial 6 months	Knee OA III/IV	73.38 ± 11.13 years	$n = 24$ (13 M/11 F) 100 U BTX-A	WOMAC	P^*: significant decrease in the WOMAC pain subscore at 3 months P^*: significant decrease in the WOMAC stiffness subscore at 5 and 6 months	0/5
Kalunian et al., [28]	RCT double blind 16 weeks	Knee OA I/II/III	62.3 years	$n = 121$(62 F/59 M)	Mean pain intensity at 2, 4, 8, 12, and 16 weeks	NS differences for the primary and secondary criteria Slight nonsignificant trend toward efficacy of BTX in the subgroup with nociceptive pain vs. neurogenic pain	5/5
Singh JA et al. [29]	RCT triple blind 6 months	Refractory pain after TKA	67 years	$n = 49$ (41 M/8 F) 100 U BTX-A ($n = 23$) Placebo ($n = 26$)	Proportion of VAS responders at 2 months	P^*: 71% of responders with BTX-A vs. 35% with placebo P^*: significant decreases in the WOMAC total score and subscores in the BTX-A group	5/5

Toxine intra-articulaire

Shu-Fen Sun et al. [30]	RCT single blind 6 months	Ankle OA	52.2 years	$n = 75$ (46 M/29 F) 100 U BTX-A ($n = 38$) Hyaluronate + 12 physiotherapy sessions, 3/week × 4	AOS	NS differences for the primary and secondary criteria	2/5

In conclusion, we reviewed the literature for data on treatment with intraarticular BTX-A in various rheumatic conditions. The studies included in our analysis have many shortcomings: they were all single-center clinical studies, and some of them exhibited methodological flaws. Proof of the anti-nociceptive effect of intraarticular BTX-A has been obtained. The good safety and tolerance profile support the use of intraarticular BTX-A.

Multicenter randomized controlled trials are needed, given the conflicting results of the studies discussed in this review. These future trials should specify the osteoarthritis grade, primary and secondary outcome measures, healthcare cost impact (e.g., use of analgesics, nonsteroidal antiinflammatory drugs, and physical therapy), and influence on quality of life and participation in social activities. The treatment modalities should be described with considerable detail (dose, dilution, injection modalities, and interval between injections). If such studies validate the therapeutic benefits of intraarticular BTX-A therapy, then further work will be needed to determine the exact position of this intervention in the therapeutic armamentarium for joint disease and, most notably, knee osteoarthritis.

In conclusion, we reviewed the literature for data on treatment with intraarticular BTX-A in various rheumatic conditions. The studies included in our analysis have many shortcomings: they were all single-center clinical studies, and some of them exhibited methodological flaws. Proof of the anti-nociceptive effect of intraarticular BTX-A has been obtained. The good safety and tolerance profile support the use of intraarticular BTX-A.

Multicenter randomized controlled trials are needed, given the conflicting results of the studies discussed in this review. These future trials should specify the osteoarthritis grade, primary and secondary outcome measures, healthcare cost impact (e.g., use of analgesics, nonsteroidal antiinflammatory drugs, and physical therapy), and influence on quality of life and participation in social activities. The treatment modalities should be described with considerable detail (dose, dilution, injection modalities, and interval between injections). If such studies validate the therapeutic benefits of intraarticular BTX-A therapy, then further work will be needed to determine the exact position of this intervention in the therapeutic armamentarium for joint disease and, most notably, knee osteoarthritis.

Efficacy of Intra-Articular Botulinum Toxin Type A in Painful Knee Osteoarthritis: A Pilot Study

PM R 2010;2:268-276

Andrea J. Boon, MD, Jay Smith, MD, Diane L. Dahm, MD, Eric J. Sorenson, MD, Dirk R. Larson, MS, Patrick D. Fitz-Gibbon, BS, Dennis D. Dykstra, MD, PhD, Jasvinder A. Singh, MD, MPH

Department of Physical Medicine and Rehabilitation, Mayo Clinic College of Medicine, Rochester, MN

Toxine intra-articulaire

Design: Double-blind, randomized, single tertiary care academic medical center trial with 6-month follow-up.

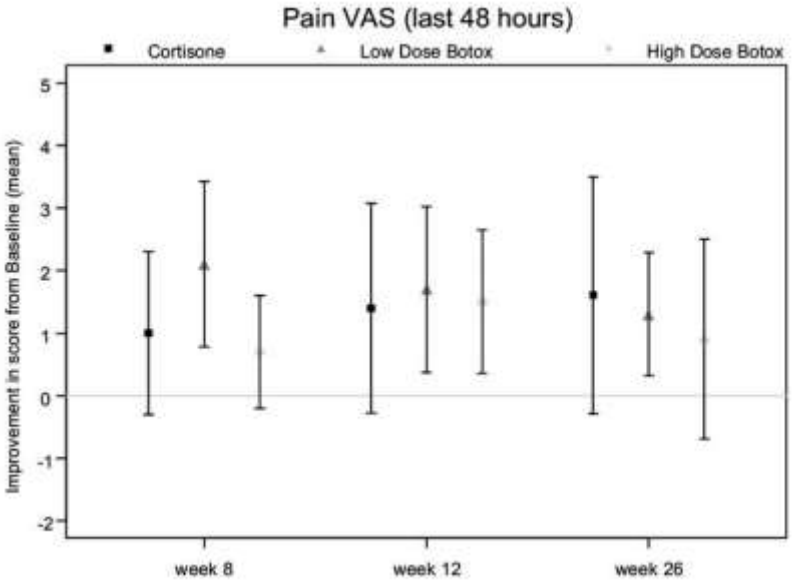
Patients: Sixty patients aged 40 years or older with painful osteoarthritis of the knee who had failed physical therapy, medications, and/or injection therapy presenting to the musculoskeletal or orthopedic outpatient clinics at a large tertiary care medical institution. All 60 patients completed 8-week follow-up, but only 32 patients completed the 26-week follow-up.

Methods: Subjects were randomized to receive a single injection of corticosteroid, low-dose BoNT-A (100 units), or high-dose BoNT-A (200 units). Outcome measures were compared at baseline, 4, 8, 12, and 26 weeks after injection.

Main Outcome Measurements: The primary outcome measure was pain visual analog scale (VAS) at 8 weeks. Secondary outcome measures included Western Ontario McMaster Arthritis Index, Short Form-36 scores, patient global assessment, 40-meter timed walk, and adverse effects.

Results: The primary end point was pain VAS score at 8 weeks, which decreased within each group but only reached statistical significance in the low-dose BoNT-A group. In the intra-articular corticosteroid group, VAS decreased from 6.4 ± 1.8 to 5.4 ± 2.3 ($P = .15$); for low-dose BoNT-A, from 6.6. ± 1.9 to 4.5 ± 2.2 ($P = .01$); and for high-dose BoNT-A, from 6.6 ± 1.4 to 5.9 ± 2.4 ($P = .15$). All groups showed statistically significant improvements in Western Ontario McMaster Arthritis Index scores (pain, stiffness, function) at 8 weeks. No serious adverse events were noted in any group.

Conclusions: This pilot study supports a possible role for BoNT-A as a treatment option for symptomatic knee osteoarthritis; however, larger double-blind randomized studies are needed to determine whether BoNT-A is more effective than placebo in this patient population.



Shu-Fen Sun , Chien-Wei Hsu , Huey-Shyan Lin , Yi-Jiun Chou ,
Jun-Yang Chen and Jue-Long Wang

Journal of Foot and Ankle Research 2014, **7**:9

JOURNAL OF FOOT AND ANKLE RESEARCH

Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: a randomized controlled trial

Background: There was an increasing requirement for novel treatments of osteoarthritis (OA). The aim was to compare the efficacy of intraarticular Botulinum toxin type A (BoNT-A) and intraarticular hyaluronate plus rehabilitation exercise in patients with ankle OA.

Methods: This was a prospective, randomized, assessor-blinded study with a 6-month follow-up period, conducted in the outpatient rehabilitation department at a university-affiliated tertiary care medical center. Seventy-five patients with symptomatic ankle OA (Kellgren-Lawrence grade 2) were randomized to receive either a single 100-unit BoNT-A injection into the target ankle (n = 38) or a single hyaluronate injection plus 12 sessions of rehabilitation exercise (30 minutes/day, 3 times/week for 4 weeks) (n = 37). The primary outcome measure was the Ankle Osteoarthritis Scale (AOS). Secondary outcome measures included American Orthopedic Foot and Ankle Society (AOFAS) Ankle/Hindfoot Score, visual analog scale (VAS) for ankle pain, single leg stance test (SLS), Timed "Up-and-Go" test (TUG), consumption of rescue analgesics and global patient satisfaction.

Results: There were no significant between-group differences in total AOS scores, pain subscale and disability subscale scores (adjusted mean difference AMD = –0.2, 95% CI = (–0.5, 0.2), p = 0.39; AMD = –0.1, 95% CI = (–0.5, 0.3), p = 0.57; AMD = –0.2, 95% CI = (–0.6, 0.2), p = 0.36). The 2 groups showed no significant differences in AOFAS, VAS, SLS, TUG scores and consumption of rescue analgesics at each follow-up visit, except that the hyaluronate group improved more in SLS than the BoNT-A group at 1-month follow-up. Patients' satisfaction rate was high, with no serious adverse events. There was no difference in adverse events between the two groups ($p = 1.00$).

Conclusions: Treatment with intraarticular BoNT-A or hyaluronate injection plus rehabilitation exercise was associated with improvements in pain, physical function and balance in patients with ankle OA. These effects were rapid at 2 weeks and might last for at least 6 months. There was no difference in effectiveness between the two interventions.

Toxine intra-articulaire

J Rheumatol. 2010 November ; 37(11): 2377–2386.

Intraarticular Botulinum Toxin A for Refractory Painful Total Knee Arthroplasty: A Randomized Controlled Trial

Jasvinder A. Singh, **Maren L. Mahowald**, and **Siamak Noorbaloochi**

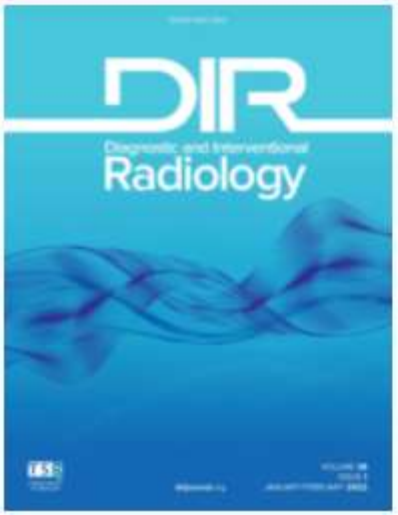
University of Minnesota, Minneapolis, Minnesota; Departments of Health Sciences Research and Orthopedics, Mayo Clinic School of Medicine, Rochester, Minnesota; Birmingham Veterans Affairs Medical Center and University of Alabama at Birmingham, Birmingham, Alabama, USA.

In this single-center randomized trial, single IA-BoNT/A injection provided clinically meaningful short-term improvements in pain, global assessment, and function in patients with chronic painful TKA. A multicenter trial is needed to confirm these findings.

Objective—To assess short-term efficacy of single intraarticular botulinum toxin (IA-BoNT/A) injection in patients with chronically painful total knee arthroplasty (TKA) in a randomized, placebo-controlled, triple-blind study.

Methods—Patients with chronic TKA pain (pain > 6 on 0–10 scale and > 6 months post-TKA) evaluated in and referred from orthopedic surgery clinics were recruited. The primary outcome, proportion of patients with clinically meaningful decrease of at least 2 points on 0–10 visual analog scale (VAS) for pain, was compared between treatment groups at 2 months using comparison of proportions test and for all efficacy timepoints (2, 3, and 4 months) using generalized estimating equations (GEE). Secondary outcomes of global assessment, function, and quality of life were compared using GEE, duration of pain relief by t-test, and adverse events by chi-square test.

Results—In total, 54 patients with 60 painful TKA were randomized, with main analyses restricted to one TKA per patient (49 TKA in 49 patients). Mean age was 67 years, 84% were men, and mean duration of TKA pain was 4.5 years. A significantly greater proportion of patients (71%) in the IA-BoNT/Agroup compared to IA-placebo (35%) achieved clinically meaningful reduction in VAS pain at 2 months ($p = 0.028$) and at all efficacy timepoints ($p = 0.019$). Duration of meaningful pain relief was significantly greater after IA-BoNT/A, 39.6 days (SD 50.4) compared to IA-placebo, 15.7 days (SD 22.6; $p = 0.045$). Statistically significantly better scores were seen in IA-BoNT/A vs IA-place-bo for all efficacy timepoints for the following outcomes: "very much improved" on physician global assessment of change ($p = 0.003$); Western Ontario McMaster Osteoarthritis Index physical function ($p = 0.026$), stiffness ($p = 0.004$), and total scores ($p = 0.024$); and Short-Form 36 pain subscale score ($p = 0.049$). Number of total and serious adverse events was similar between groups, with no patients in either group with new objective motor or sensory deficits during followup.



Piriformis syndrome: pain response outcomes following CT-guided injection and incremental value of botulinum toxin injection

Kevin Yan [1], Yin Xi [1], Rocco Hlis [1], Avneesh Chhabra [1 2]

Diagn Interv Radiol 2021; 27: 126-133
DOI: 10.5152/dir.2020.19444

CONCLUSION

CT-guided injections with botulinum toxin for patients with piriformis syndrome are more likely to lead to a positive response and a longer duration of response than patients who receive a CT-guided injection without botulinum toxin. We hope that this study facilitates future prospective randomized blind trials for patients with suspected piriformis syndrome.

Effectiveness of botulinum toxin for treatment of symptomatic pelvic floor myofascial pain in women: A systematic review and meta-analysis

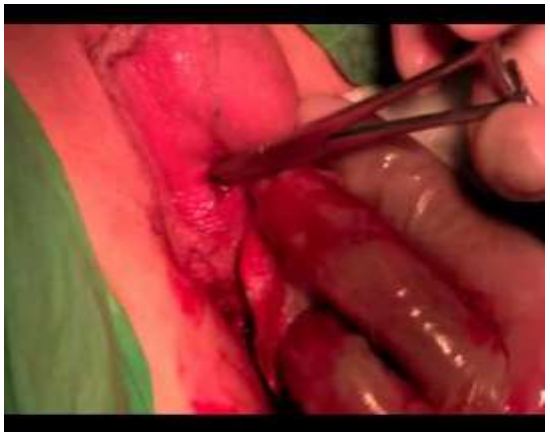
Melanie R. MEISTER, Allison BRUBAKER, Siobhan SUTCLIFFE, Jerry L. LOWDER,

Female Pelvic Med Reconstr Surg. 2021 January 01; 27(1): e152–e160. doi:10.1097/SPV.0000000000000870.

FPMRS
Female Pelvic Medicine & Reconstructive Surgery

Results: A statistically significant reduction in patient-reported pain scores was noted at 6 weeks after botulinum toxin injection (mean difference 20.3, 95% CI 11.7 – 28.9) and continued past 12 weeks (mean difference 19.4, 95% CI 14.6 – 24.2). Significant improvement was noted in secondary outcomes including dyspareunia, dyschezia, and quality of life.

A propos d'une douleur chronicisée cicatricielle et de l'usage de la toxine botulique A



Viel EJ, Mares P, Pages A, Jedryka F
Soumis à publication
Female Pelvic Med Reconstr Surg 2022

DNP post-chirugicale…muqueuse
Bartholinite / hématome / surinfection

toxins

MDPI

Article

Monocentric Prospective Study into the Sustained Effect of Incobotulinumtoxin A (XEOMIN®) Botulinum Toxin in Chronic Refractory Migraine

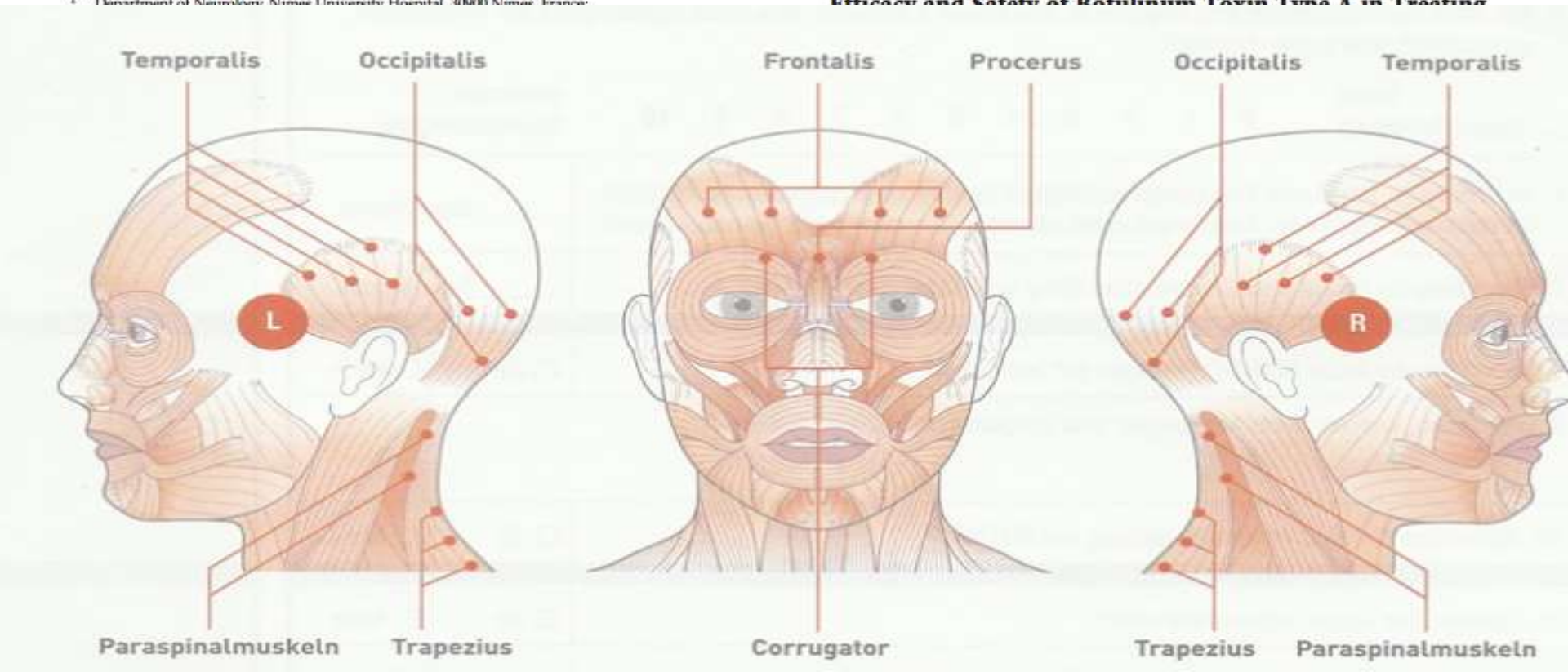
Ioana Ion [1,*], Dimitri Renard [1], Anne Le Floch [1], Marie De Verdal [1], Stephane Bouly [1], Anne Wacongne [1], Alessandro Lozza [2] and Giovanni Castelnovo [1]

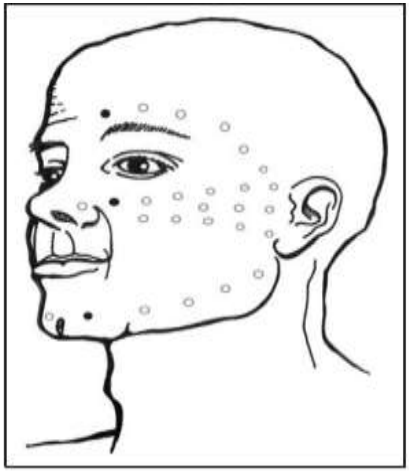
1 Department of Neurology, Nimes University Hospital, 30900 Nimes, France;

Hindawi
Pain Research and Management
Volume 2018, Article ID 7365148, 5 pages
https://doi.org/10.1155/2018/7365148

Clinical Study

Efficacy and Safety of Botulinum Toxin Type A in Treating





Effects of Botulinum Toxin Type A on Pain among Trigeminal Neuralgia, Myofascial Temporomandibular Disorders, and Oromandibular Dystonia

Kazuya Yoshida

Dystonia. *Toxins* **2021**, *13*, 605. https://doi.org/10.3390/toxins13090605

toxins

Abstract: The differences in analgesic effects of botulinum toxin type A were compared in 28 patients with trigeminal neuralgia, 53 patients with myofascial temporomandibular disorders, and 89 patients with the jaw closing oromandibular dystonia. The patients were treated by injection of botulinum toxin type A into the masseter, temporalis, medial pterygoid, and other muscles based on the symptoms of each patient. The pain severity was evaluated using the visual analog scale, pain frequency, and pain scale of the oromandibular dystonia rating scale. Botulinum toxin injection was performed 1068 times in all patients without significant adverse effects. The visual analog, pain frequency, and pain scales at baseline were reduced ($p < 0.001$) after two, four, eight, and 12 weeks after the first botulinum toxin therapy and at the endpoint. The effects differed significantly ($p < 0.001$) among the groups (repeated-measures analysis of variance). The mean improvement (0%, no effect; 100%, complete recovery) at the endpoint was 86.8% for trigeminal neuralgia, 80.8% for myofascial pain, and 75.4% for oromandibular dystonia. Injection of the botulinum toxin can be a highly effective and safe method to treat trigeminal neuralgia, myofascial pain, and oromandibular dystonia.

ıfa

patients

m published

N.

RCTs on the

nders (risk

ncy per day

1; $I^2 = 36$ %).

CONCLUSION:

Despite limited data, our results suggest that BTX-A may be an effective and safe treatment option for patients with TN. Further larger and well-designed RCTs are encouraged to translate these findings into better clinical outcome and better quality of life for TN patients.


LA RÉVOLUTION, CE N'EST NI UN DÎNER MONDAIN,
NI UN ÉVÉNEMENT LITTÉRAIRE.
LA RÉVOLUTION EST UN ACTE DE VIOLENCE.
IL ÉTAIT
UNE FOIS LA
RÉVOLUTION

Practice Guideline › Rev Neurol (Paris). 2020 May;176(5):325-352.
doi: 10.1016/j.neurol.2020.01.361. Epub 2020 Apr 7. X Moisset et al

Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations

Neuropathic pain

Focal peripheral NP

Other peripheral or central NP

1st line

lidocaine plasters
TENS

or

duloxetine
gabapentin
tricyclic antidepressants

2nd line

capsaicin 8 % patch
Botulinum toxin A

or

pregabalin
venlafaxine
tramadol
Combination therapy

3rd line

pulsed radiofrequency
spinal cord stimulation

or

strong opioids
HF-rTMS of M1

Psychotherapy

French recommendations Nov 2019 National meeting SFETD

pharmaceutics

Pharmaceutics **2021**, *13*, 450. https://doi.org/10.3390/pharmaceutics13040450

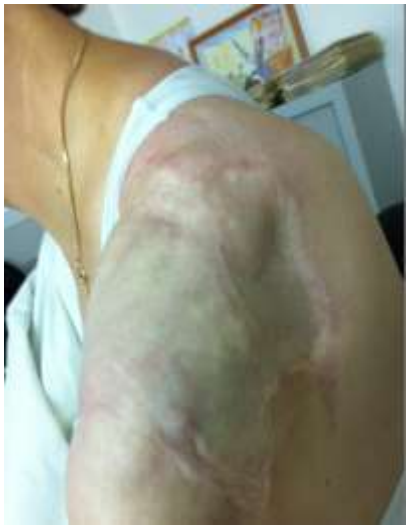
MDPI

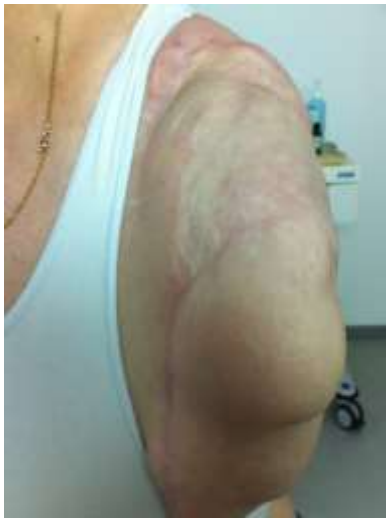
Review

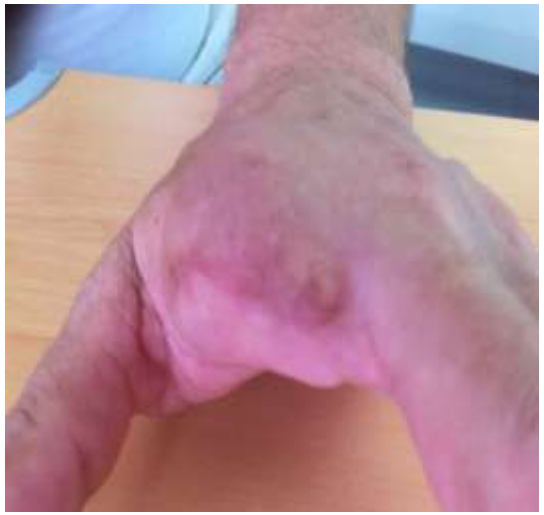
Topical Treatments and Their Molecular/Cellular Mechanisms in Patients with Peripheral Neuropathic Pain—Narrative Review

Magdalena Kocot-Kępska [1,*], Renata Zajączkowska [2], Joanna Mika [3], David J. Kopsky [4,5], Jerzy Wordliczek [2], Jan Dobrogowski [1] and Anna Przeklasa-Muszyńska [1,*]

The evidence from RCTs and reviews supports 5% lidocaine patches, 8% capsaicin patches, and botulinum toxin A injections as effective treatments in patients with peripheral neuropathic pain.







Toxicon

Volume 147, 1 June 2018, Pages 120-128

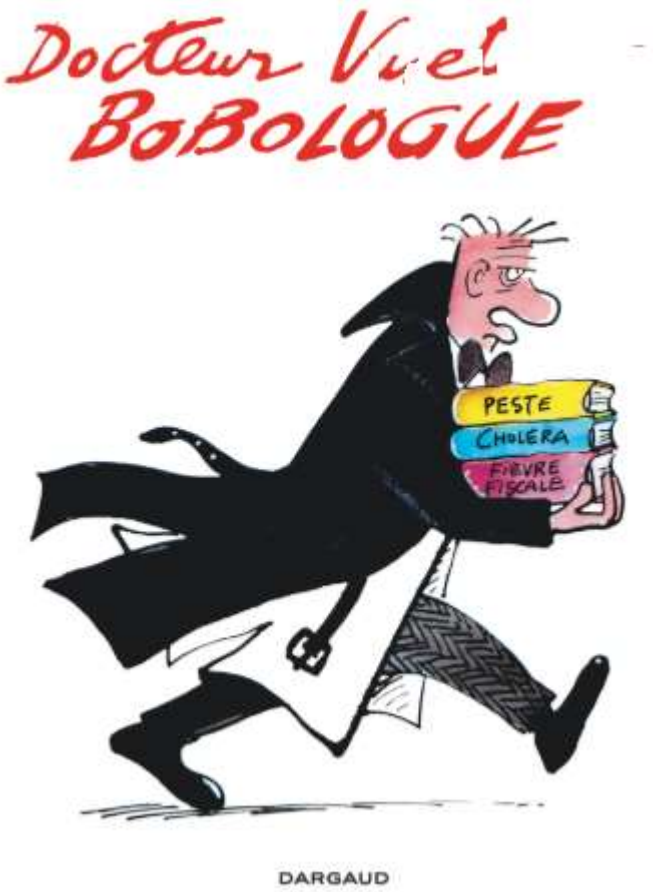
Botulinum toxin treatment of pain syndromes –an evidence based review

Yasaman Safarpour , Bahman Jabbari

This review evaluates the existing level of evidence for efficacy of BoNTs in different pain syndromes using the recommended efficacy criteria from the Assessment and Therapeutic Subcommittee of the American Academy of Neurology. There is a level A evidence (effective) for BoNT therapy in post-herpetic neuralgia, trigeminal neuralgia, and posttraumatic neuralgia. There is a level B evidence (probably effective) for diabetic neuropathy, plantar fasciitis, piriformis syndrome, pain associated with total knee arthroplasty, male pelvic pain syndrome, chronic low back pain, male pelvic pain, and neuropathic pain secondary to traumatic spinal cord injury. BoNTs are possibly effective (Level C -one class II study) for female pelvic pain, painful knee osteoarthritis, post-operative pain in children with cerebral palsy after adductor release surgery, anterior knee pain with vastus lateralis imbalance. There is a level B evidence (one class I study) that BoNT treatment is probably ineffective in carpal tunnel syndrome. For myofascial pain syndrome, the level of evidence is U (undetermined) due to contradicting results. More high quality (Class I) studies and studies with different types of BoNTs are needed for better understanding of the role of BoNTs in pain syndromes.

En résumé… les douleurs neuropathiques périphériques

1. des données d'efficacité
2. des recommandations
3. une gradation des H.d.J.
4. la réserve hospitalière
5. des indications hors-A.M.M.
6. un moratoire



Merci de votre attention

Incobotulinum Toxin For Refractory Neuropathic Pain Following Breast Cancer Surgery

Authors' Names: François Jedryka[a], Eric J.Viel[a*], Maryline Laigre[b], Hélène Codderens[b], Caroline Gallay[b], Jesus Diaz[b], Philippe Cuvillon[b,c],

Authors' Affiliations (italicized): [a] *Pain Clinic, University Hospital, Nîmes, France;* [b] *Department of Supportive Care, Regional Cancer Institute, Montpellier, France;* [C] *Department of Anesthesiology, University Hospital, Nîmes, France;*
***Corresponding author:** *Pain Clinic, University Hospital Caremeau, eric.viel@chu-nimes.fr , Nîmes, 30029, France.*

Review

The Expanding Therapeutic Utility of Botulinum Neurotoxins

toxins

Elena Fonfria [1,*], Jacquie Maignel [2], Stephane Lezmi [2], Vincent Martin [2], Andrew Splevins [1], Saif Shubber [3], Mikhail Kalinichev [2], Keith Foster [1], Philippe Picaut [4] and Johannes Krupp [2]

Received: 13 April 2018; Accepted: 16 May 2018; Published: 18 May 2018

Characteristics of current major botulinum neurotoxin (BoNT) products.

	AboA [1]	IncoA [2]	OnaA [3]	RimaB [4]
1st Approval	1991	2005	1989	2000
Serotype	A1	A1	A1	B
Strain	Hall	Hall	Hall	Bean
Purification Method s	Chromatography	Unpublished	Crystallization	Chromatography
Complex Size	>500 kD	150 kD	900 kD	700 kD
Excipients	HSA (125 µg) Lactose	HSA (1 mg) Sucrose	HSA (500 µg) Sodium chloride	HSA (500 µg/mL) Sodium succinate Sodium chloride
Stabilization	Lyophilization	Lyophilization	Vacuum drying	Solution
Solubilization	Normal saline	Normal saline	Normal saline	N/A
pH	~7	~7	~7	5.6
Unitage (U/vial)	300, 500	100, 200	100, 200	2500, 5000, 10,000
Shelf Life (months)	24	36	36	24
Neurotoxin Protein (ng/vial) †	4.35	0.6	5	~25, 50, 100

† Protein (ng/vial) is for entire neurotoxin complex, the total protein load being dominated by albumin. HSA = human serum albumin. [1] AboA = abobotulinumtoxinA (Dysport®). Dysport® PI, Ipsen, 2015. [2] IncoA = incobotulinumtoxinA (Xeomin®). Xeomin® PI, Merz, 2015. [3] OnaA = onabotulinumtoxinA (Botox®). Botox® PI, Allergan, 2015. [4] RimaB = rimabotulinumtoxinB (Myobloc®/Neurobloc®). Myobloc® PI, Worldwide Meds, 2010.