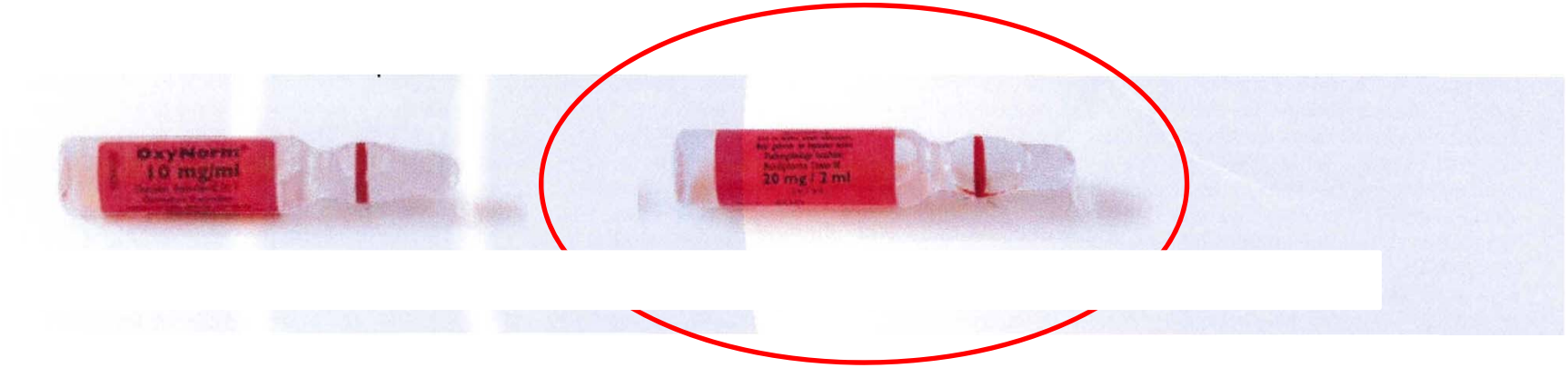

Quoi de neuf, docteur?
Dr Nathalie MATHIEU
Anesthésiologie
Coordination CMETD

News

- Médicaments
- MEOPA en cancérologie
- Patch capsaicine
- Mirror box
- Hypnose
- Approche nutritionnelle
- Musicothérapie

Oxynorm®

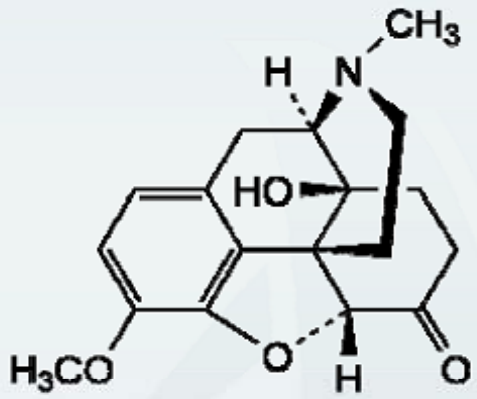
- Comprimé oxycodone: IR, SR
- Ampoule
  - Disponible en Belgique:
    - 2ml/en concentration de 10mg/ml (4.5 eur/amp)
  - En attente: 50mg/ml (pour dilution perfusion)
- Attention: dilution stable seulement 24h



Targinact®

Oxycodone Meets Naloxone

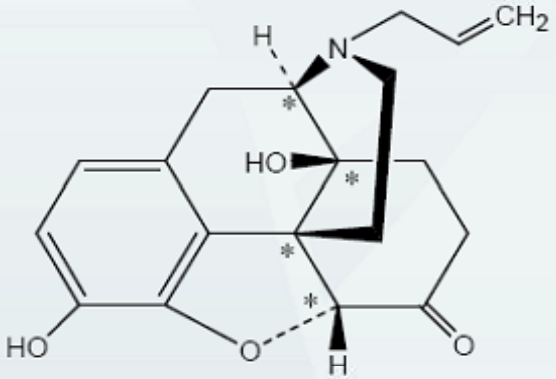
Oxycodone



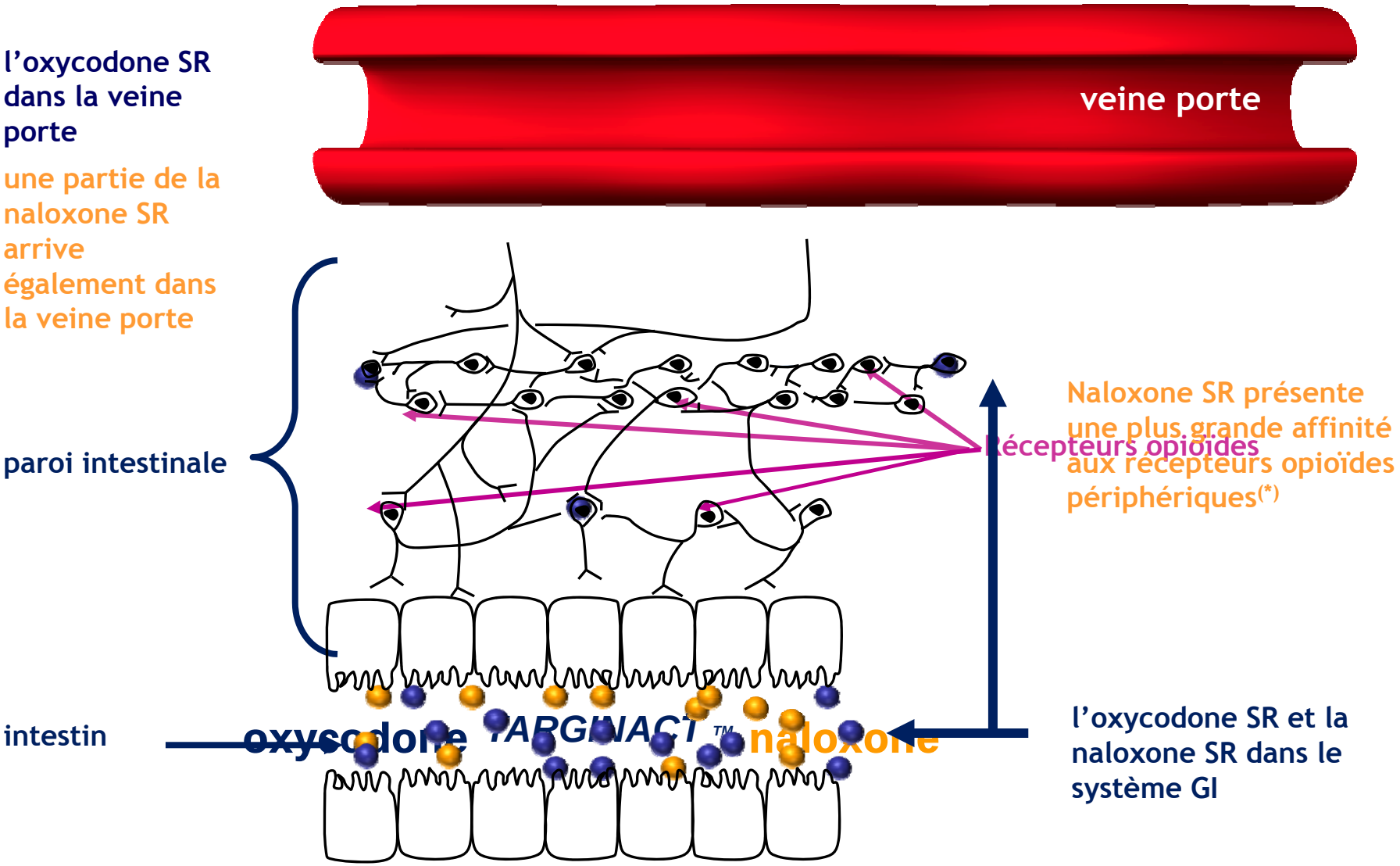
, HCl

+

Naloxone



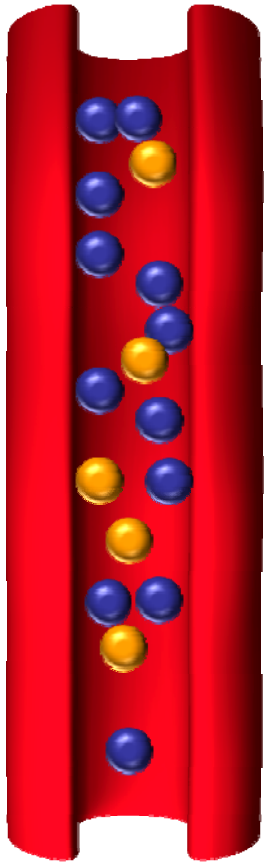
, HCl, 2 H_2O



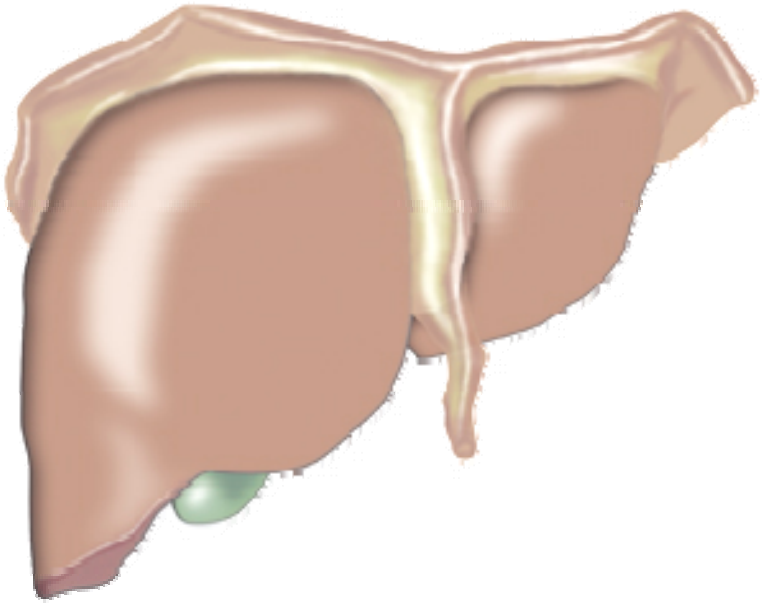
d'après: Kurz A et al. Drugs 2003;63:649–71 [3]

le foie– facteur important [3]

oxycodone
naloxone
absorbés

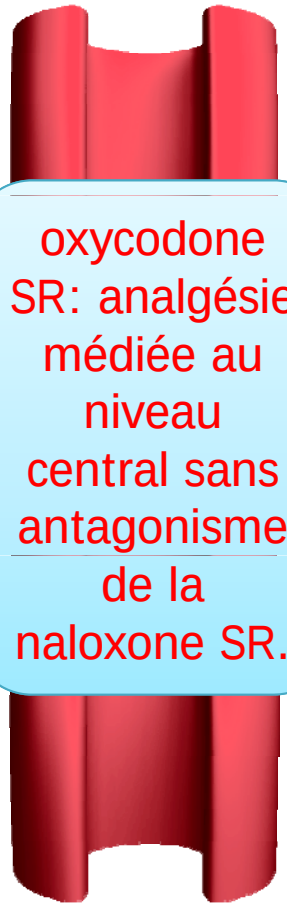


veine porte



oxycodone SR: ≤ 87% inchangé dans la circulation systémique

naloxone SR : > 97% éliminé durant la métabolisation de premier passage



oxycodone SR: analgésie médiée au niveau central sans antagonisme de la naloxone SR.

circulation systémique

3. **Kurz A et al**. Drugs 2003;63:649–71

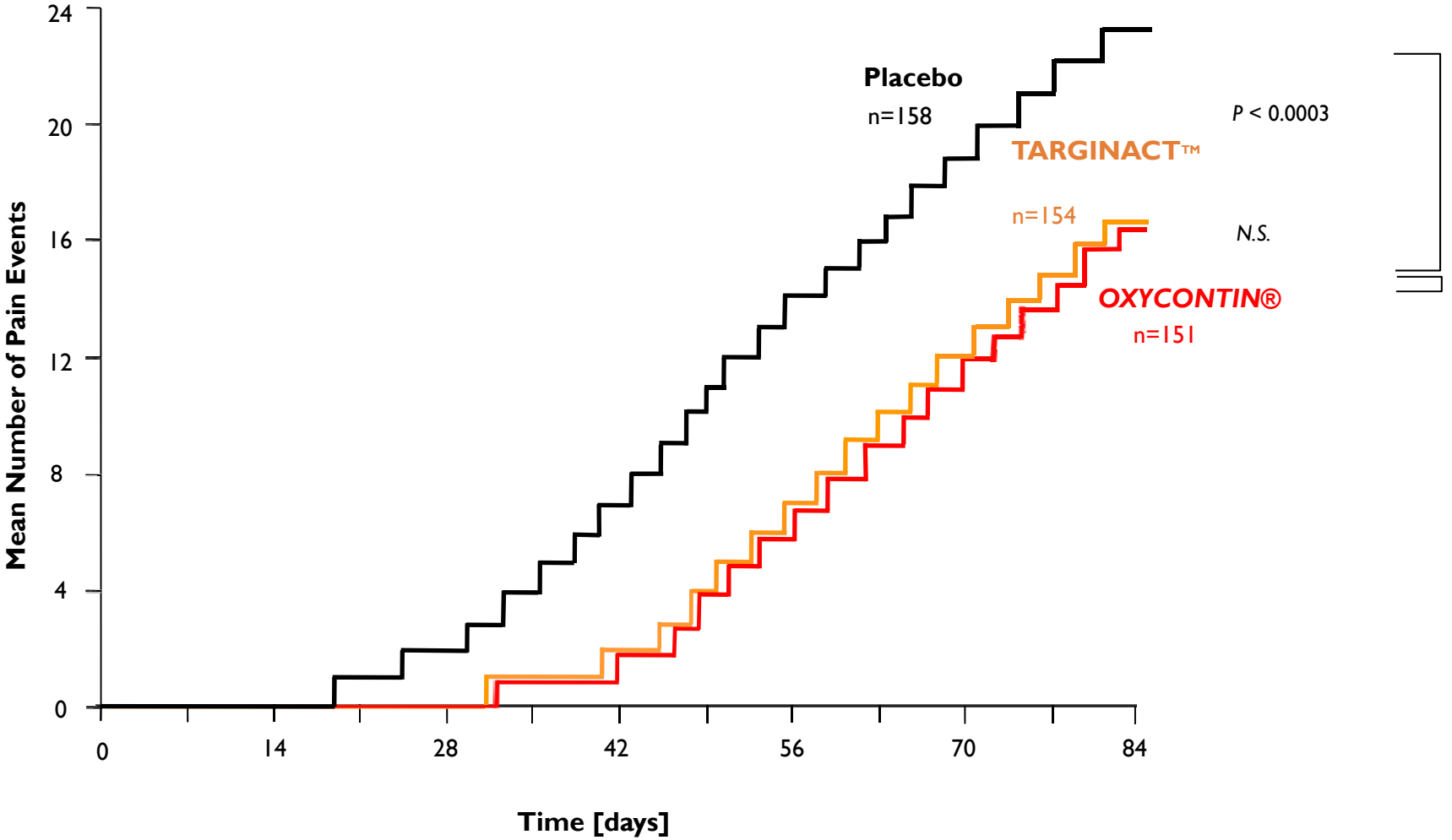
indication officielle (1)

“La douleur sévère ne pouvant être traitée de manière adéquate que par des analgésiques opioïdes. La naloxone, un antagoniste opioïde, est ajoutée afin de lutter contre la constipation induite par les opioïdes en inhibant l’effet de l’oxycodone sur les récepteurs opioïdes locaux du tube digestif. ”

(1) SPC

ANALGESIC EFFICACY

OXN 3401



Vondrackova D et al. J Pain 2008;9:1144–54

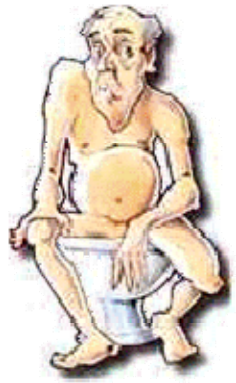
Mesure de la fonction intestinale

BFI (Bowel Function Index)

- **Facilité à déféquer**
  au cours des sept derniers jours avant la consultation
  (NAS: 0 = facile- 100 = difficulté importante)

- **Sensation d'évacuation incomplète de l'intestin**
  au cours des sept derniers jours avant la consultation
  (NAS: 0 = aucune- 100 = très forte)

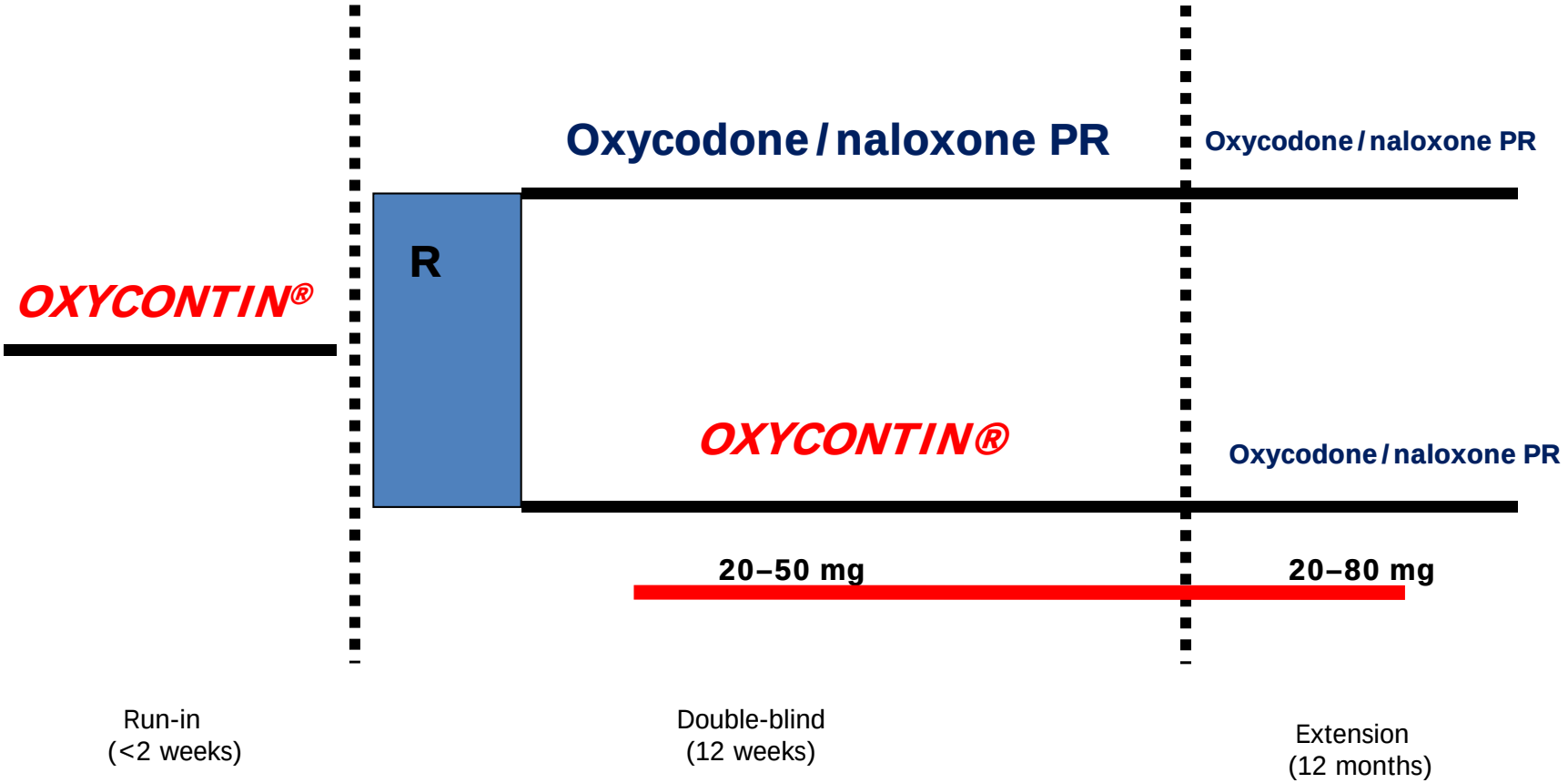
- **Avis personnel du patient concernant sa constipation**
  au cours des sept derniers jours avant la consultation
  (NAS: 0 = aucune - 100 = très forte)



BFI Moyen = Moyenne de ces trois variables

Rentz A.M. **Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation**. Journal of Medical Economics *2009*, **12**(4), 371-383.

BOWEL FUNCTION

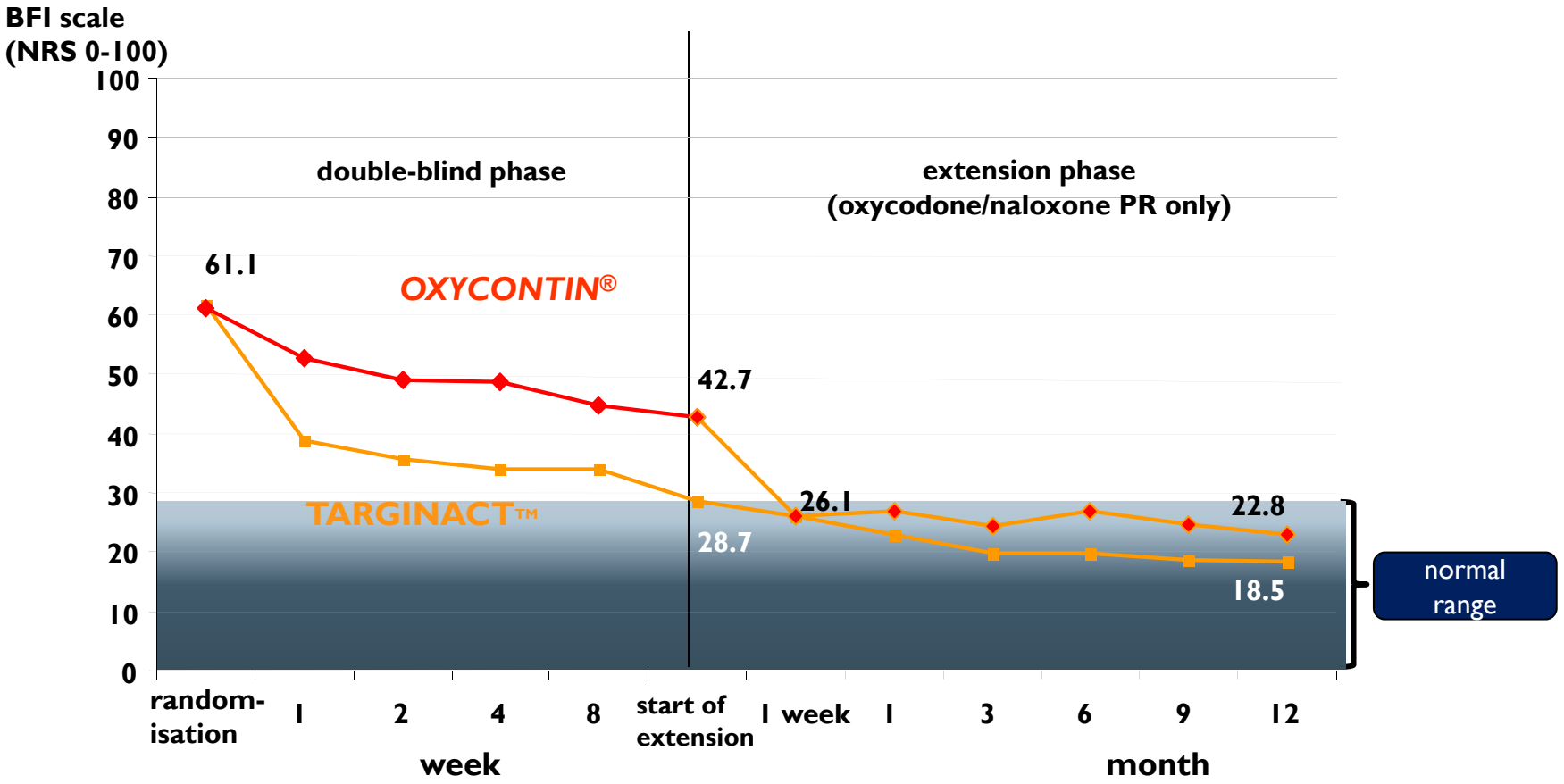


Primary outcome measure – BFI

Doses of oxycodone/naloxone PR up to 40/20 mg per day are currently licensed for use

Simpson K et al. Curr Med Res Opin 2008;24:3503-12

BOWEL FUNCTION



Doses of oxycodone/naloxone PR up to 40/20 mg per day are currently licensed for use

Simpson K et al. Curr Med Res Opin 2008;24:3503-12
Meissner W et al. World Institute of Pain, New York. 2009. Abstract A-118-0027-00784

TARGINACT
OXYCODONE/NALOXONE

- rapport oxycodone/naloxone: 2 sur 1 [1]
- Naloxone n'influence pas action analgésique de l'oxycodone[2]
- prophylaxie de la constipation induite par opioïdes

5mg/2,5mg
10mg/5mg
20mg/10mg
40mg/20mg

30 comprimés

Opiorphine

- Découverte en 2006 (équipe Catherine Rougeot)
- =inhibiteur physiologique des ectopeptases dégradant les enképhalines
- = active aussi la transmission opiacée physiologique
- Avril 2010: synthèse d'un dérivé fonctionnel identique et stable
- Septembre 2010: (études s/rat)
  - Aussi puissante que M+ mais ES moindre(pas constipation, accoutumance)
  - Aussi effficace que imipramine (antidépresseur) sans ses ES (hyperexcitation, sédation)

J Physiology Pharmacology 2010;61(4):483-90
J Physiology Pharmacology 2010;61(3):355-62

MEOPA en cancérologie

- « Prise en charge de la douleur au cours des procédures invasives en cancérologie: efficacité et acceptabilité du mélange inhalé 50% N2O/02 »
  - Randomisée, en double insu, EVA éinitiale et max pdt le geste
  - 30% des 199 patients avaient fond D+ permanent
  - Acceptabilité par patient et équipe: 89%
  - La D+ maximale ressentie durant le geste< de 10mm vs placebo p=0.012

Krakowski, Baylot, Lossignol et Billoët, Douleur analg. 2010; 23:113-120

QUTENZA®

An application system containing 8% capsaicin that is optimised for rapid dermal delivery

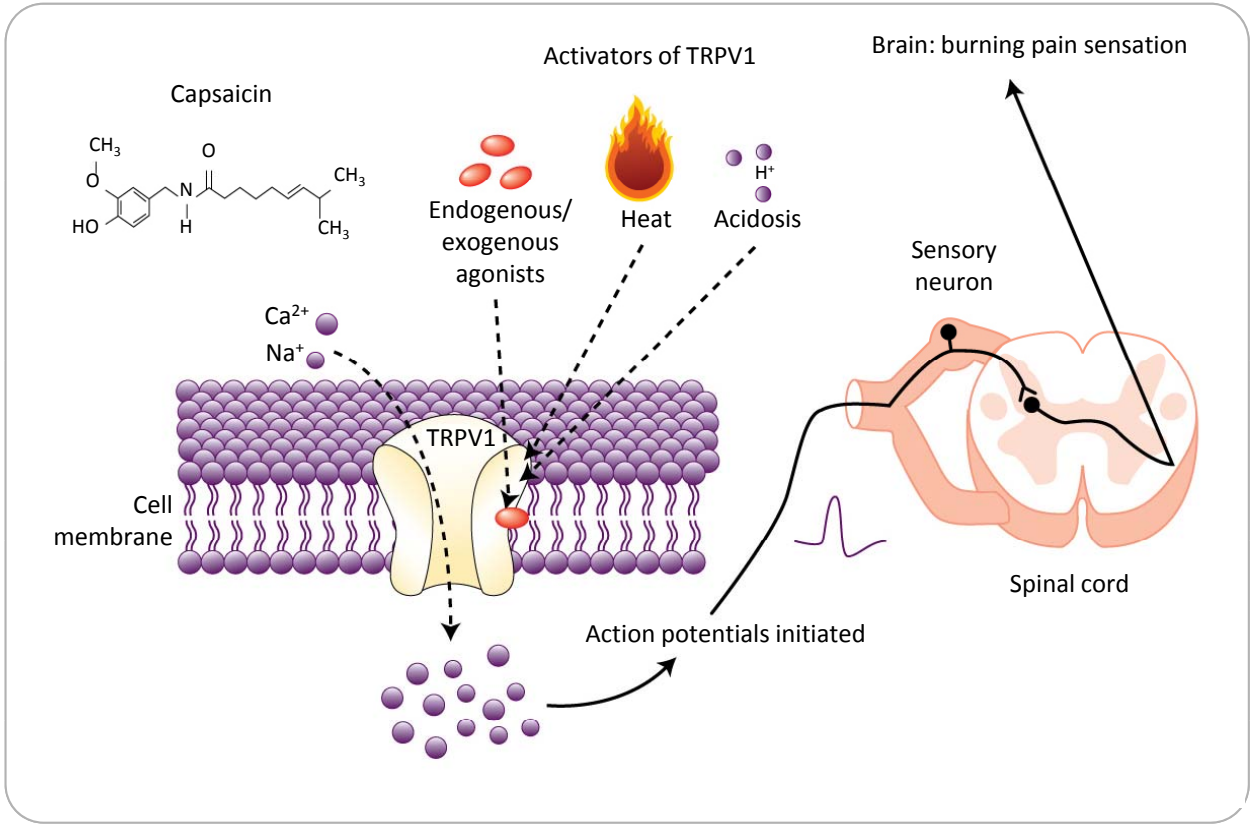
A single 30- or 60-minute application delivers prolonged relief of neuropathic pain for 3 months

Works by rapidly delivering a high dose of capsaicin to 'defunctionalise' hyperactive nociceptors in the skin

Indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain

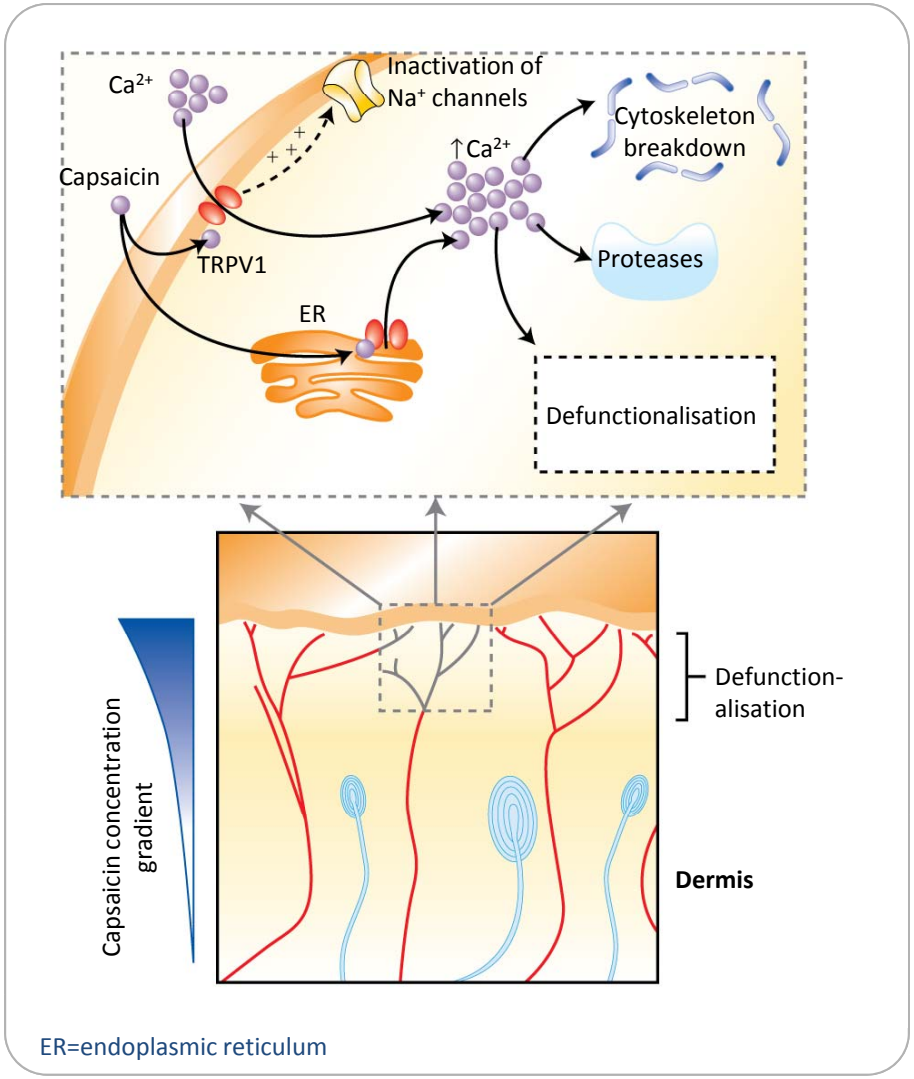
Transient Receptor Potential Vanilloid 1 (TRPV1) receptors

- Expressed in nociceptors[1,2]
- Key receptor involved in pain sensation[1]
- Activated by various stimuli (including capsaicin) to produce a pain response[2]



1. Caterina MJ, Julius D. Annu Rev Neurosci 2001;24:487–517; 2. Premkumar LS, Sikand P. Curr Neuropharmacol 2008;6:151–163

Why use capsaicin for neuropathic pain?



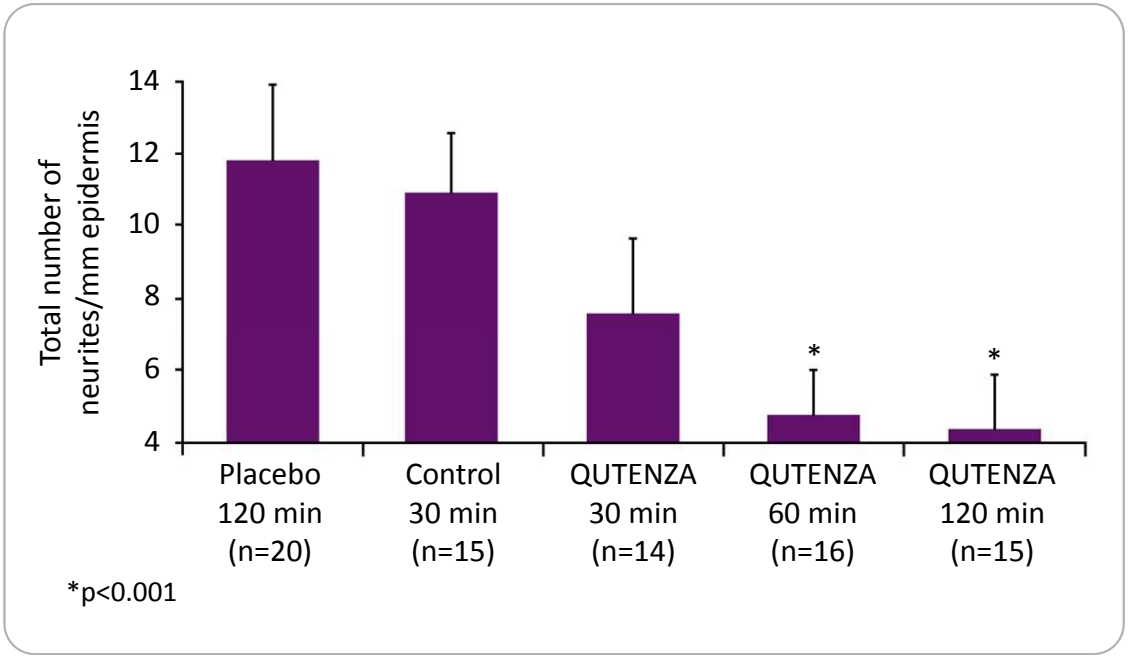
ER=endoplasmic reticulum

- **Capsaicin — TRPV1 agonist[1]**
- **TRPV1 activation:**
  - **Ca^{2+} and Na^{+} move into the nociceptor[2]**
- **Continuous TRPV1 activation:**
  - **Ca^{2+} influx activates Ca^{2+}-sensitive proteases + other mechanisms**
  - **Defunctionalisation of nociceptors[3,4]**
  - **Neurite degeneration — nociceptors 'recede' from the epidermis[3,4]**

1. Caterina MJ, Julius D. Annu Rev Neurosci 2001;24:487–517; 2. Rosenbaum T, et al. J Gen Phys 2002;123:53–64; 3. Nolano M, et al. Pain 1999;81(1-2):135–145; 4. Premkumar LS, Sikand P. Curr Neuropharmacol 2008;6(2):151–163

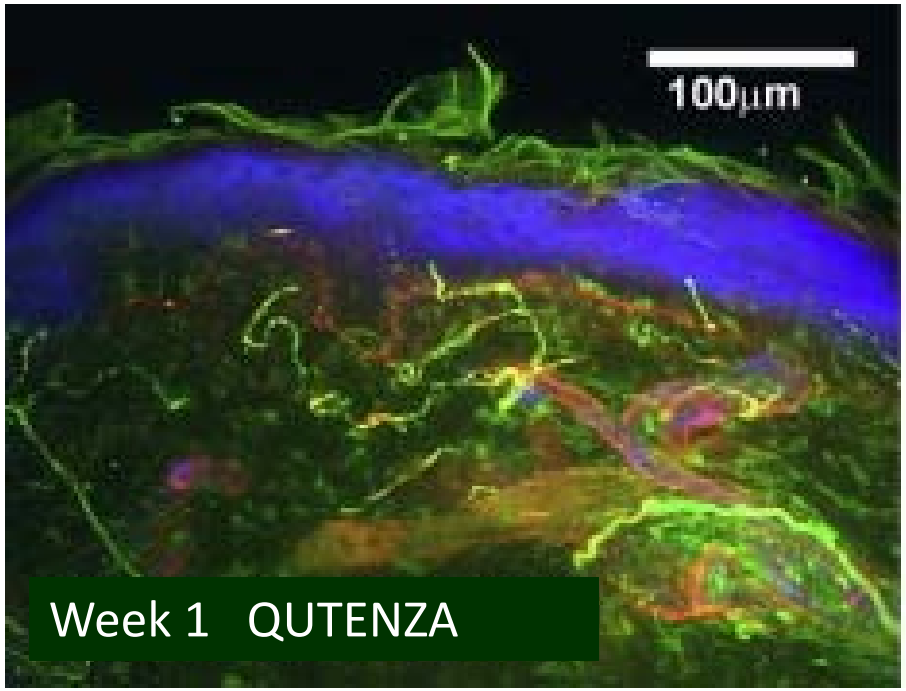
Phase I Study C101

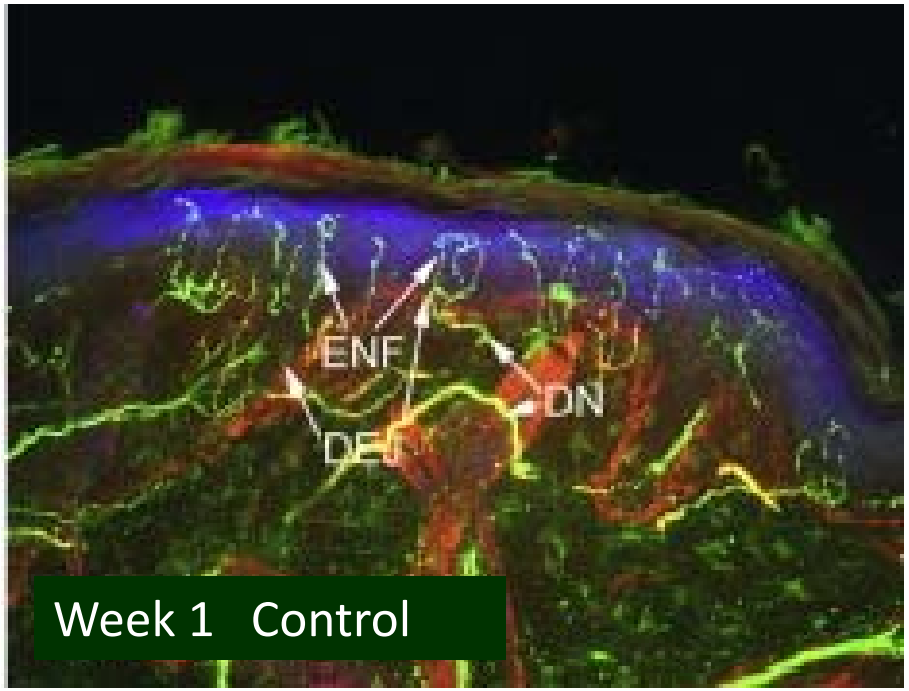
- QUTENZA significantly decreased epidermal nerve fibre (ENF) density by ~60%



Malmberg AB, et al. Pain 2004;111(3):360–367

Visualising capsaicin-induced defunctionalisation



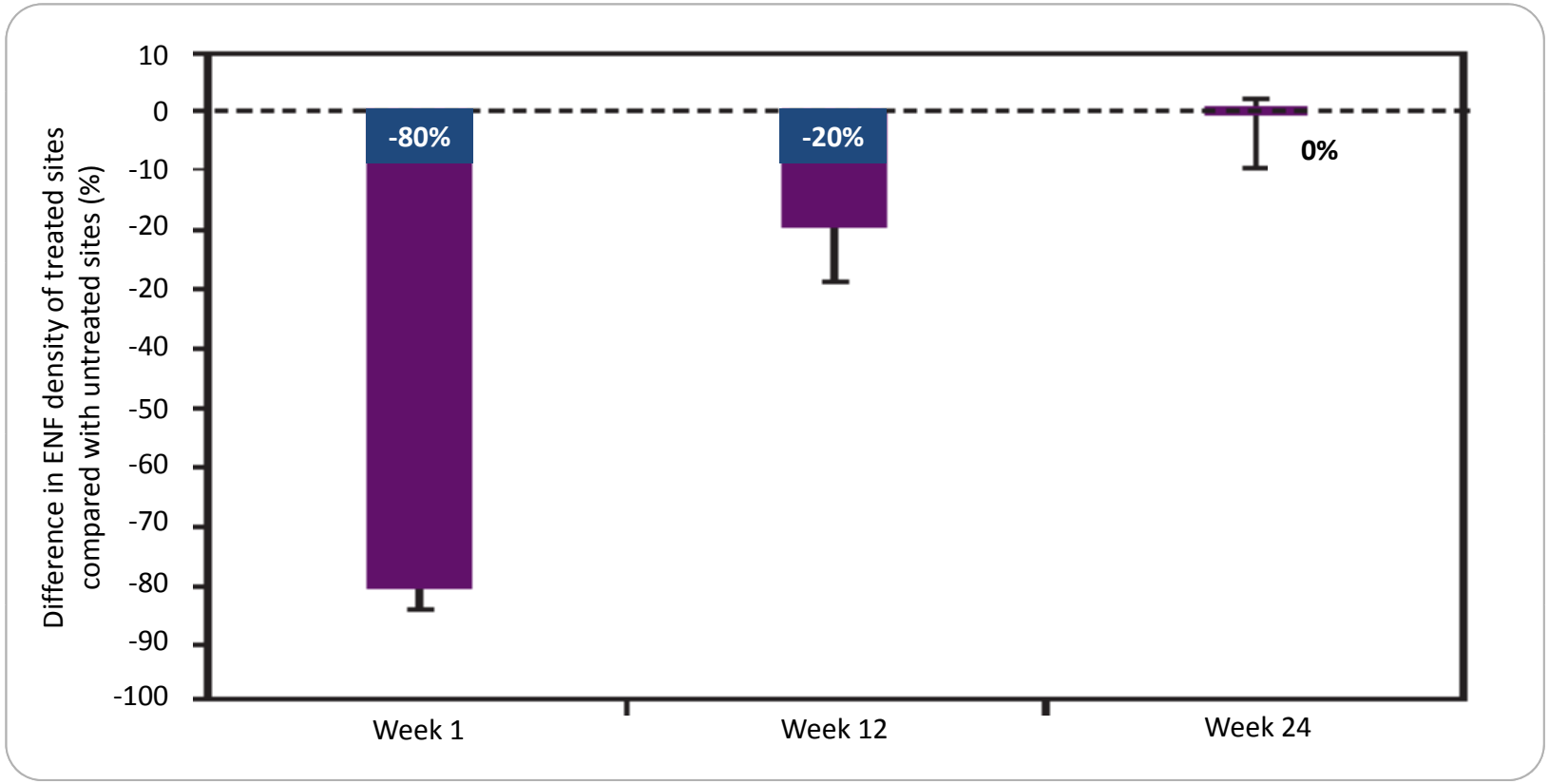


ENF=epidermal nerve fibre; DN=dermal nerve; DEJ=dermal–epidermal junction

Kennedy WR, et al. J Pain 2010; Apr 16 [Epub ahead of print]

Phase I Study C115

- ENF density recovers fully 24 weeks after QUTENZA



Data on file. [047]. 2009. Astellas Pharma Europe Ltd.

Pharmacokinetics

Parameter	Geometric mean
$T_{1/2}$, hours	1.64
60 minutes	
AUC, ng.h/mL	4.36
C_{max}, ng/mL	1.38
T_{max}, hours	1.46
90 minutes	
AUC, ng.h/mL	7.77
C_{max}, ng/mL	2.96
T_{max}, hours	1.51

AUC=area under the curve of plasma concentration versus time; C_{max}=peak plasma concentration; T_{max}=time to the peak plasma concentration; $T_{1/2}$=terminal elimination half-life.

Evaluation of 173 patients receiving QUTENZA for 90 or 60 minutes[1]

34 samples had quantifiable capsaicin levels for analysis[1]

- Following QUTENZA application, there is minimal absorption of capsaicin through the skin[2]
  - **The maximum plasma concentration is less than that observed following consumption of chilli peppers**

1. Babbar S, et al. Ther Drug Monit 2009;31(4):502–510; 2. QUTENZA SPC (EMA). 2009

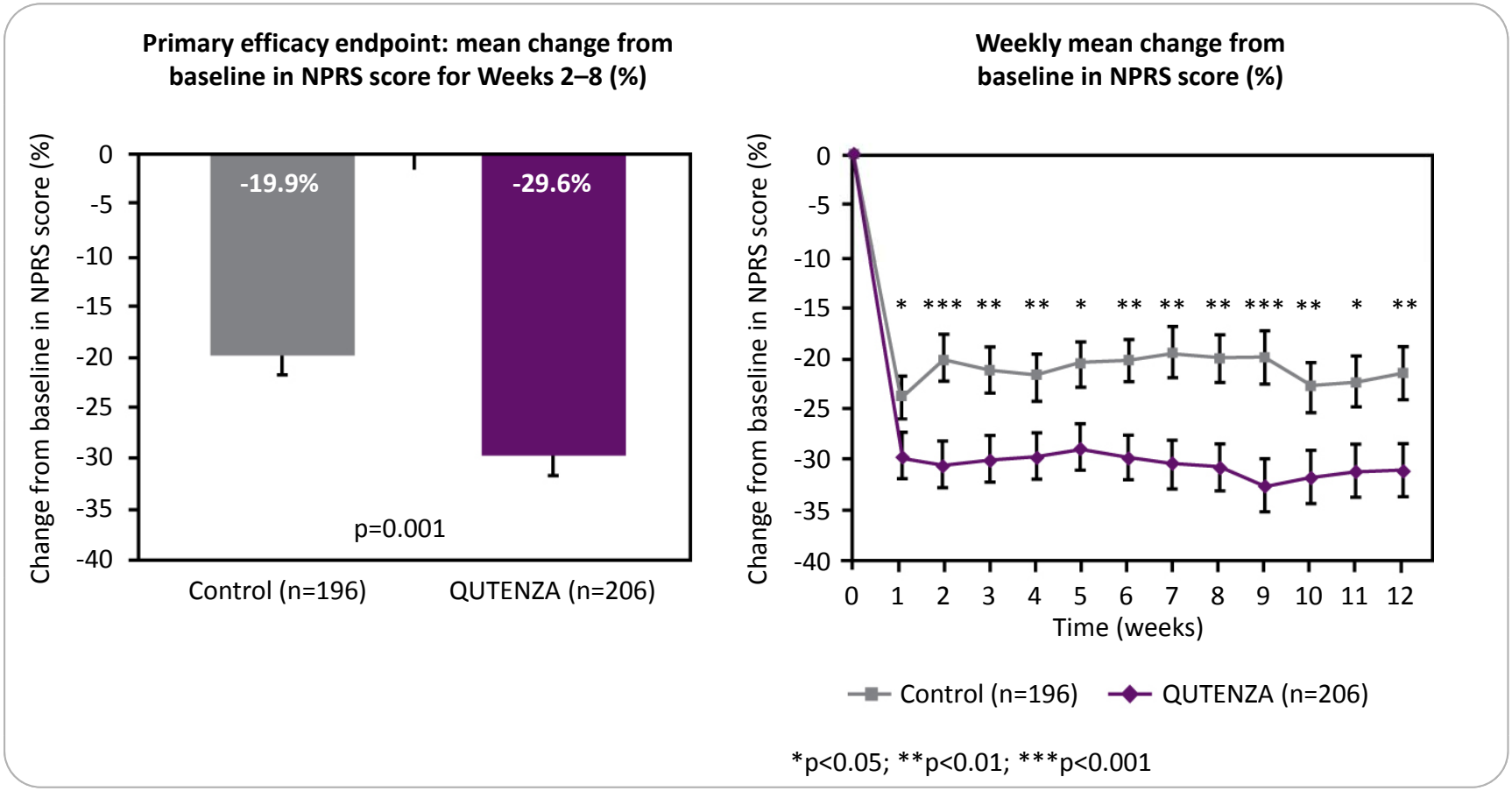
Phase III: Pivotal trials in PHN

- Multicentre, randomised, double-blind, controlled,
  12-week Phase III studies
- Single 60-minute application of QUTENZA
- Total of 818 patients with PHN of ≥6 months post vesicle crusting

Backonja M, et al. Lancet Neurol 2008;7(12):1106–1112; Data on file [054]. Astellas Pharma Europe Ltd 2009.

PHN Study: Overall pain reduction

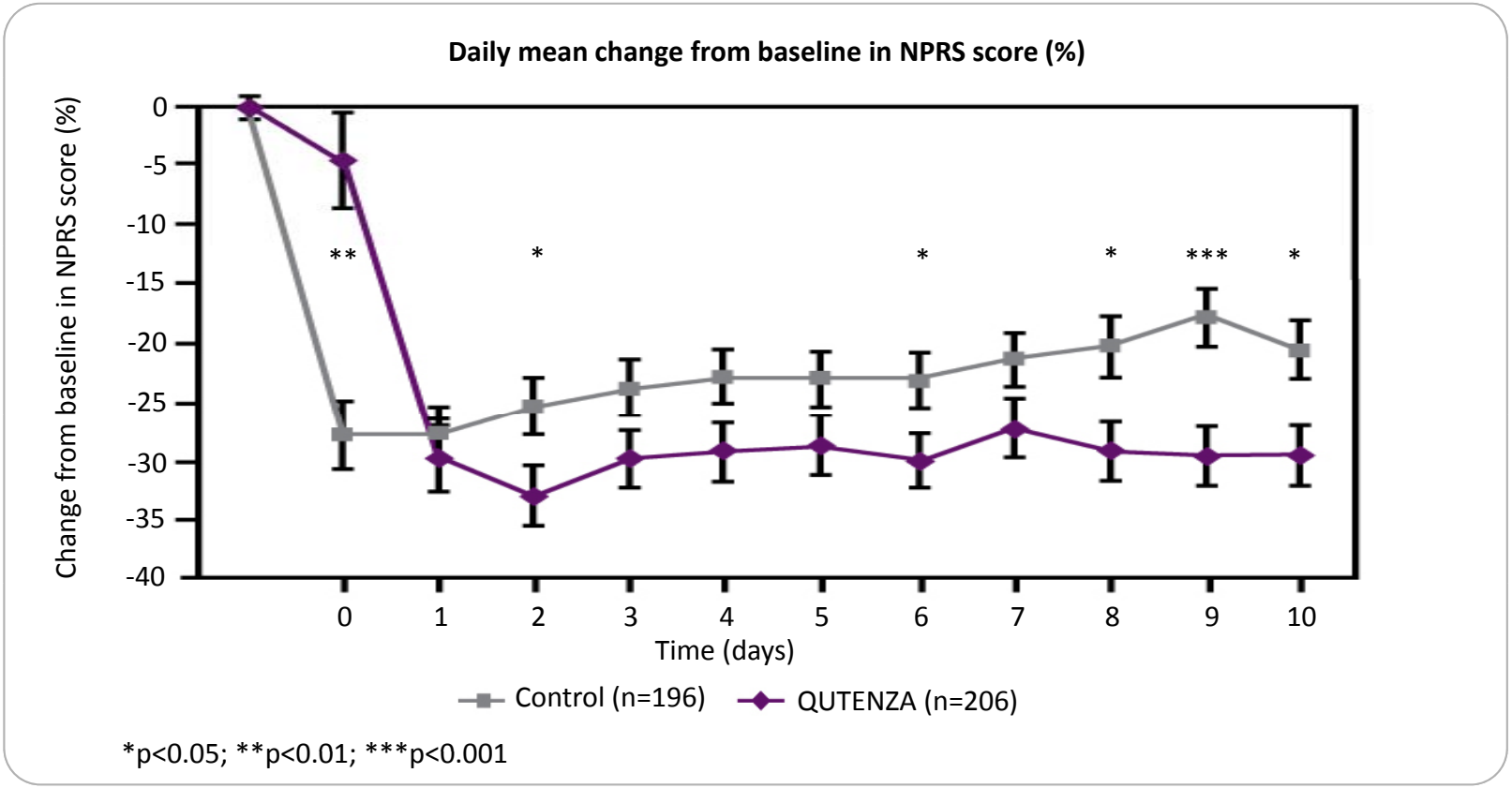
- QUTENZA results in prolonged pain relief for 12 weeks



Backonja M, et al. Lancet Neurol 2008;7(12):1106–1112

PHN Study: Daily pain reduction

- QUTENZA results in rapid pain relief within 2 days following application



Backonja M, et al. Lancet Neurol 2008;7(12):1106–1112

Summary of efficacy in PHN

- Prolonged pain relief for 12 weeks from a single 60 minutes application of QUTENZA in patients with PHN
- Rapid onset of action with pain relief as early as Day 2
- Significant pain relief when used as monotherapy
- Significant incremental improvement in pain when added on to other neuropathic pain medications

Backonja M, et al. Lancet Neurol 2008;7(12):1106–1112

Summary of efficacy in HIV

- Prolonged efficacy from a single 30 minute application in HIV-AN
- Clinically significant pain relief by Week 2 after treatment
- Significant pain relief with QUTENZA as monotherapy and in combination with other neuropathic pain treatments
- Consistent and reproducible efficacy with up to 4 treatments during a 52-week period

Simpson DM, et al. Neurology 2008;70(24):2305–2313

QUTENZA: Most common AEs

QUTENZA AEs are predominantly application site related

Event	QUTENZA (n=1327) %	Control (n=789) %
Dryness	3.5	0.9
Erythema	42.9	41.6
Pain	45.5	22.2
Papules	4.9	2.0
Pruritus	7.8	4.1
Swelling	3.3	1.8

Data on file [044]. 2009. Astellas Pharma Europe Ltd.

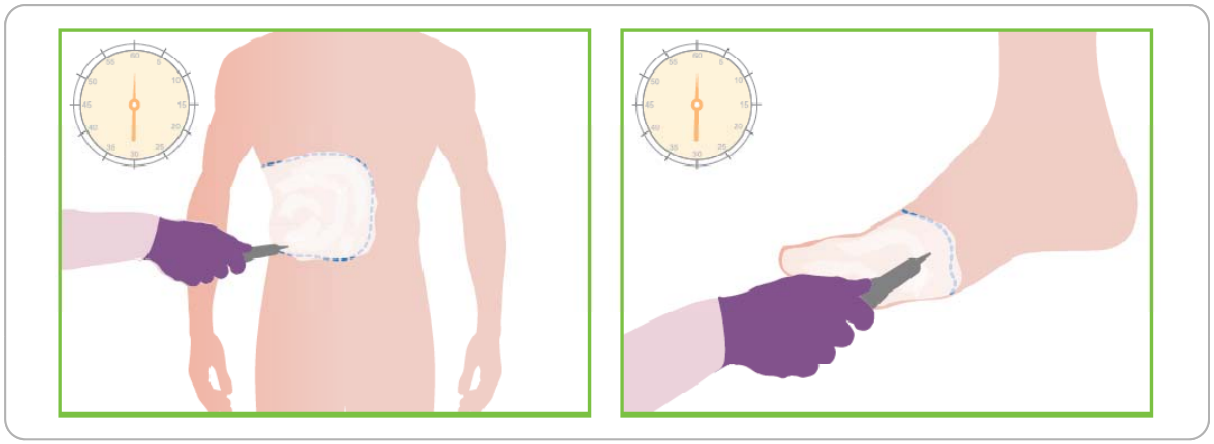
Application **precautions** for QUTENZA

- For application by physicians/healthcare professionals only
  - Use nitrile not latex gloves
- Avoid aerosolisation and manual contamination
- Monitor blood pressure
- May need opioid alternatives for opioid-tolerant patients
- Minor transient changes in sensory function observed in healthy volunteers
- Cleansing gel (butylhydroxyanisole) may cause skin reactions or irritation

QUTENZA SPC (EMA). 2009

Administration: Identify and anaesthetise

- Identify and mark the area to be treated (cut hair, do not shave)
- Anaesthetise: — pretreat the entire area + surrounding 1–2 cm with topical anaesthetic

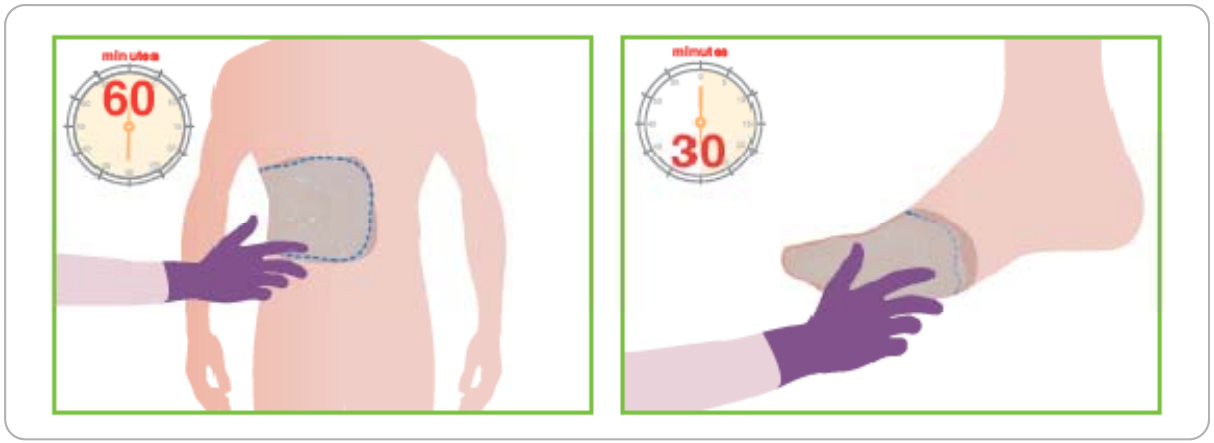


Remove the anaesthetic cream before applying QUTENZA

QUTENZA SPC (EMA). 2009

Administration: Apply

- Cut the film; peel and fold a section of the release liner and place the adhesive side of the film on the treatment area
- Hold in place; then slowly and carefully peel away the release liner while smoothing the film onto the skin



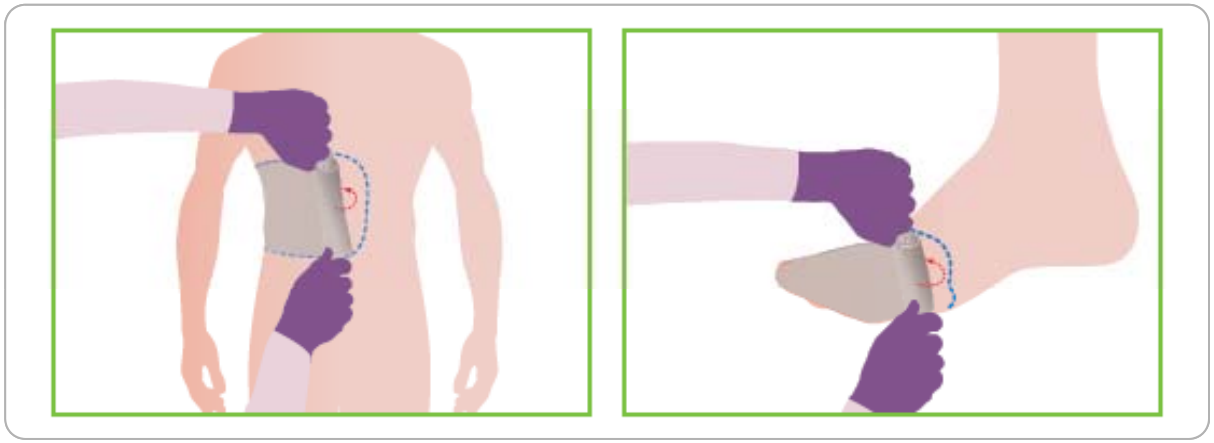
Allow the film to remain in place for:

- **30 minutes for the feet**
- **60 minutes for any other area**

QUTENZA SPC (EMA). 2009

Administration: Remove, cleanse and advise

- Remove: slowly and gently remove the QUTENZA film by rolling it inward to minimise the risk of aerosolisation of capsaicin



Cleanse: apply cleansing gel liberally and leave on for at least 1 minute. Wipe off cleansing gel with dry gauze and gently wash the area with soap and water

Advise: inform the patient that the treated area may be sensitive (to heat, hot showers/baths, direct sunlight, vigorous exercise, etc.) for a few days

QUTENZA SPC (EMA). 2009

Pain 130 (2007) 294–298

PAIN

www.elsevier.com/locate/pain

Clinical note

Using visual illusion to reduce at-level neuropathic pain in paraplegia

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Received 21 September 2006; received in revised form 4 January 2007; accepted 10 January 2007

Abstract

Neuropathic pain after spinal cord injury is not well understood and is difficult to treat. One possible cause is mismatch between motor commands and sensory feedback. This two-part study in five paraplegic patients investigated whether a visual illusion aimed to correct this mismatch reduces pain. In study 1, patients undertook three conditions: (i) virtual walking: with a mirror placed in front of a screen, patients aligned their own upper body with a film of a lower body walking. Patients imagined walking and 'watched themselves' walk; (ii) guided imagery; (iii) watching a film. One patient withdrew from virtual walking because of distress. For all patients, the mean (95% CI) decrease in pain (100 mm VAS) was 42 mm (~65%) (11–73 mm) for virtual walking, 18 mm(4–31 mm) for guided imagery and 4 mm (−3 to 11 mm) for watching the film. Mean (95% CI) time to return to pre-task pain was 34.9 min (20.1–49.8 min) for virtual walking; 13.9 min (−0.9 to 28.8 min) for the guided imagery and 16.3 min (1.5–31.2 min) for the film. To investigate its clinical utility, four patients underwent virtual walking every weekday for 3 weeks. Mean (95% CI) decrease in pain was 53 mm (45–61 mm) at post training and 43 mm (27–58 mm) at 3-month follow-up. Virtual walking may be a viable treatment for pain after spinal cord injury. A clinical trial seems warranted.

Keywords: Spinal cord injury; Physical therapy; Neuropathic pain; Paralysis; Visual input; Sensory-motor incongruence

1. Introduction

and rectum. Because the pain is associated with lesion

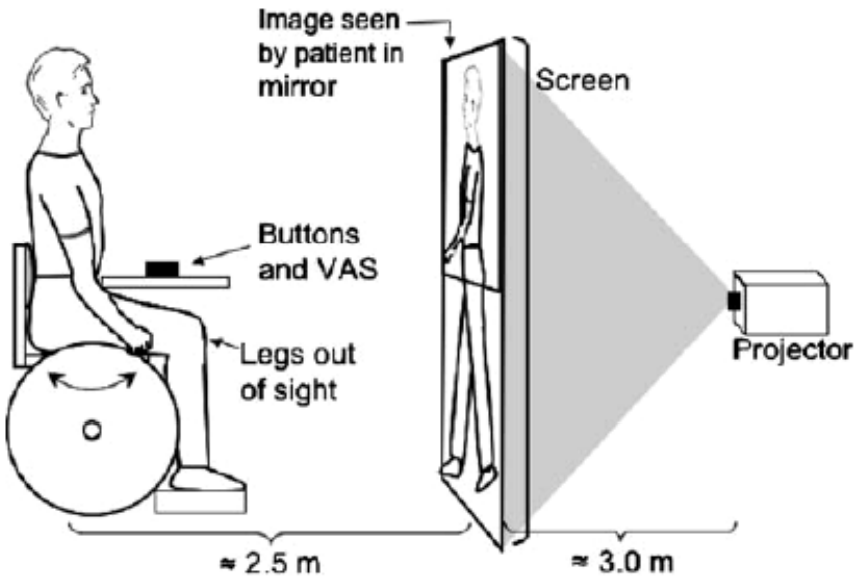

Fig. 1. Experimental set-up. The film was projected onto the screen. For virtual walking, a mirror was placed in front of the upper half of the screen so that, in the patient's view, their own upper body was aligned with the lower body in the film. Patients rated the intensity of their pain on an electronic visual analogue scale (VAS) by pressing a left or right button. The VAS and buttons were placed on a board that obstructed view of the legs.

Pain 114 (2005) 54–61

PAIN

www.elsevier.com/locate/pain

Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial

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Received 11 August 2004; received in revised form 9 November 2004; accepted 15 November 2004

Abstract

In complex regional pain syndrome (CRPS1) initiated by wrist fracture, a motor imagery program (MIP), consisting of hand laterality recognition followed by imagined movements and then mirror movements, reduces pain and disability, but the mechanism of effect is unclear. Possibilities include sustained attention to the affected limb, in which case the order of MIP components would not alter the effect, and sequential activation of cortical motor networks, in which case it would. Twenty subjects with chronic CRPS1 initiated by wrist fracture and who satisfied stringent inclusion criteria, were randomly allocated to one of three groups: hand laterality recognition, imagined movements, mirror movements (RecImMir, MIP); imagined movements, recognition, imagined movements (ImRecIm); recognition, mirror movements, recognition (RecMirRec). At 6 and 18 weeks, reduced pain and disability were greater for the RecImMir group than for the other groups ($P < 0.05$). Hand laterality recognition imparted a consistent reduction in pain and disability across groups, however, this effect was limited in magnitude. Imagined movements imparted a further reduction in pain and disability, but only if they followed hand laterality recognition. Mirror movements also imparted a reduction in pain and disability, but only when they followed imagined movements. The effect of the MIP seems to be dependent on the order of components, which suggests that it is not due to sustained attention to the affected limb, but is consistent with sequential activation of cortical motor networks.

Keywords: Cortical reorganisation; Chronic pain; Reflex sympathetic dystrophy; Motor cortex; Pre-motor cortex; Physiotherapy

La « mirror (pain) box »

Hypnose

- L'*autohypnose* représente l'utilisation par soi-même des états modifiés de conscience

- Elle permet de modifier ses programmations négatives et de donner des nouvelles perspectives à sa vie.

Hypnose

- La **douleur** physique (aiguë et répétitive) et morale
- La **confiance en soi**
- Gestion des **troubles de la personnalité**
- **Troubles anxieux**
- **angoisses**
- Gestion du **stress**
- **Dépression**
- **Phobies** : phobies scolaires, sociales, etc.
- Problématique de **deuil,** phase d'acceptation d'un deuil
- V**iolences (physiques et psychologiques)**
- Les séquelles de **traumatismes**

Hypnotherapy for the management of chronic pain

- Elkins G, Jensen MP, Patterson D: Int J Clin Exp Hypn. 2007 Jul;55(3):275-87.
- **14 studies**, excluding studies of headaches,
- The findings indicate that hypnosis interventions consistently produce **significant decreases in pain associated with a variety of chronic-pain problems.**
- **Also, hypnosis was generally found to be more effective than nonhypnotic interventions such as attention, physical therapy, and education.**
- Most of the hypnosis interventions for chronic pain include instructions in s**elf-hypnosis**.
- But: lack of standardization of the hypnotic interventions , the number of patients enrolled in the studies has tended to be low and lacking long-term follow-up

Chronic pain syndromes and their treatment by psychological interventions

- Curr Opin Psychiatry. 2009 Mar;22(2):200-4.
- Kröner-Herwig B.

- SUMMARY: Regarding different pain syndromes such as **chronic back pain, headache, fibromyalgia, and temporomandibular disorder**, as well as gastrointestinal pain in children, psychological interventions proved their significance for the achievement of favourable treatment outcome

Approche nutritionnelle

- Alimentation anti-inflammatoire
  - Prévention !!!!
    - Mal bouffe depuis des années!
  - Amélioration des symptômes inflammatoires
  - Modification de son alimentation et si nécessaire prise de compléments alimentaires ciblés en fonction des carences et des pathologies
  - Dr Frédéric LOUIS…..

La musicothérapie

- consiste à utiliser la musique comme outil thérapeutique, pour rétablir, maintenir ou améliorer la santé mentale, physique et émotionnelle d'une personne.
- *Autre version*: Benenzon, qui considère que la musicothérapie est une psychothérapie non-verbale

Assessment and standardisation of a new music therapy technique in the management of pain: The “U-based” system

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- Introduction
- De nombreuses études soulignent l’intérêt de la musicothérapie dans le traitement de la douleur. Le montage en « U » est une technique de musicothérapie développée en tenant compte des recommandations de la littérature. Un logiciel a été réalisé au CHRU de Montpellier avec la société Music Care© permettant son utilisation standardisée par les soignants.
- Résultats
- L’effet de la musicothérapie a été évalué sur différents types de douleurs aiguës et chroniques d’origines diverses : mécaniques, inflammatoires, fibromyalgiques et neurologiques. Une action physiologique (sur les paramètres hémodynamiques et respiratoires, etc.) mais aussi psychologique, en favorisant la relation d’« écoute » entre soignant et soigné, a ainsi pu être mise en évidence. Cette action se traduit par une réduction de la douleur, de l’anxiété et de la dépression permettant une baisse significative des consommations d’anxiolytiques et d’antidépresseurs.
- Internet: www.musicotherapie-amarc.org/

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