Traitement des douleurs neuropathiques
Présent, futur

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Centre d'Evaluation et de Traitement de la Douleur
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92100 Boulogne-Billancourt, FRANCE

Caen, 12 juin 2019

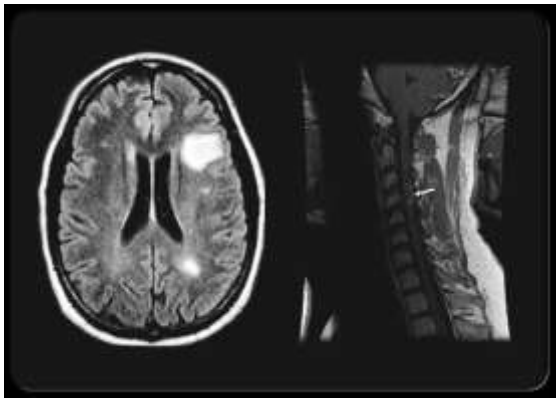
Déclaration d'intérêt

Honoraires de MSD, Sanofi, Aptinyx, Grunenthal, Lilly, Pfizer, Astellas, Teva sur les 5 dernières années

Douleurs neuropathiques

Zona

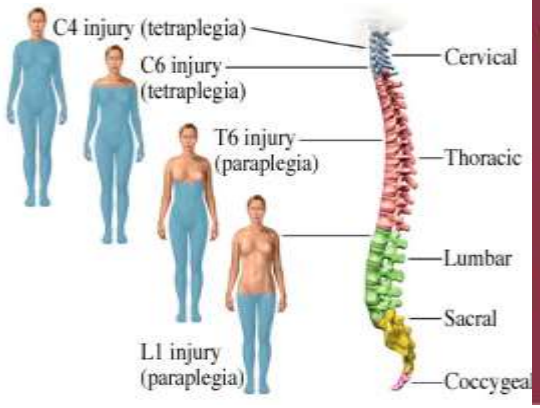
Chirurgie



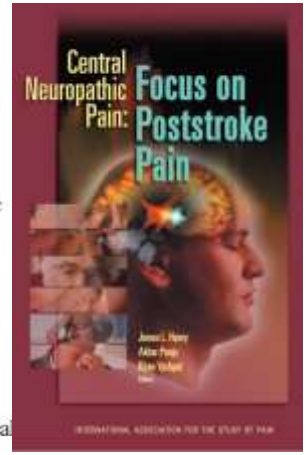
SEP

Polyneuropathie

Sciatique

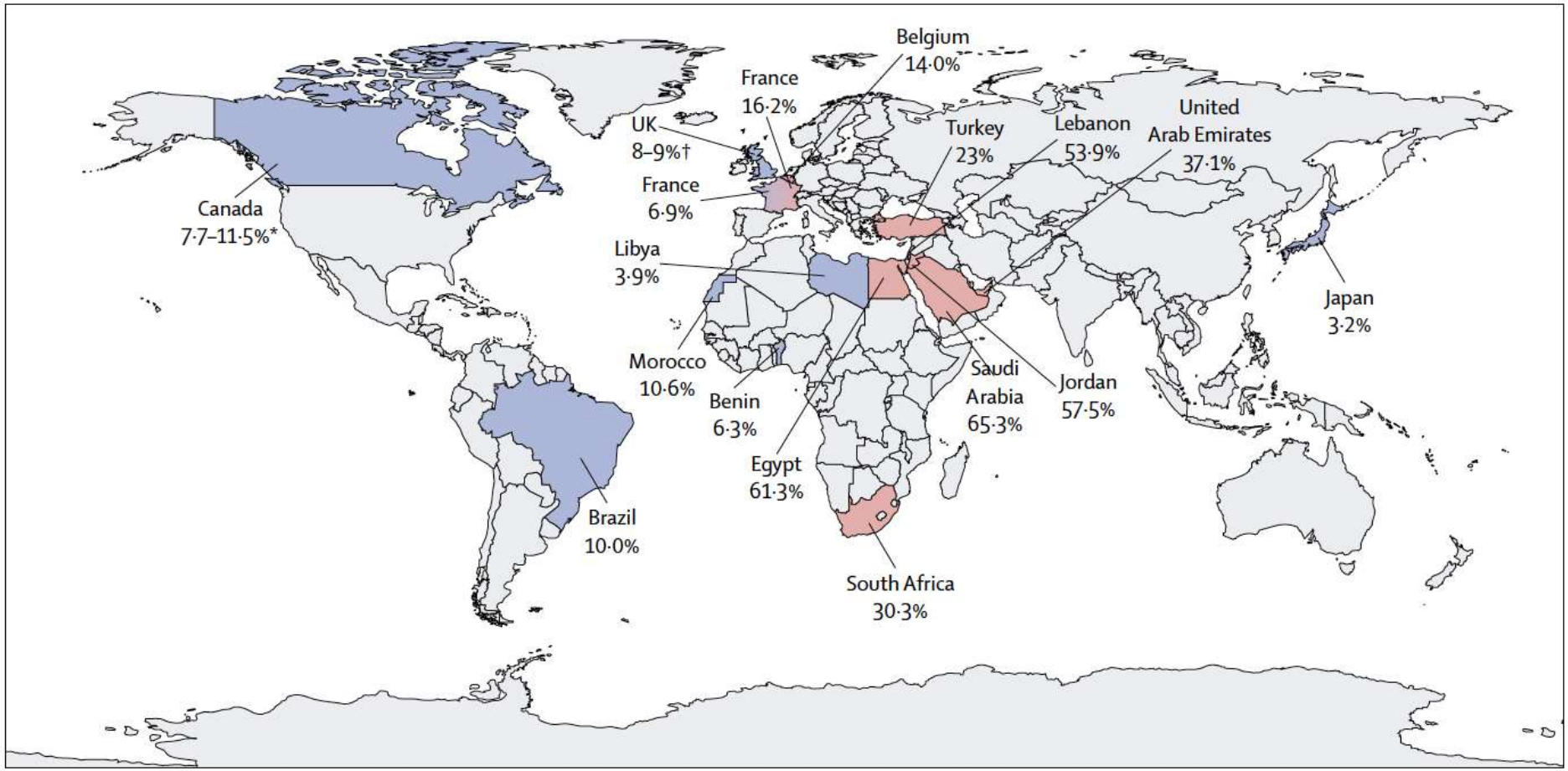


Lésion médullaire



AVC

Prévalence de la douleur neuropathique dans le monde



Population générale

Neuropathie diabétique

Attal et al Lancet Neurol 2018

PAIN® 152 (2011) 2836–2843

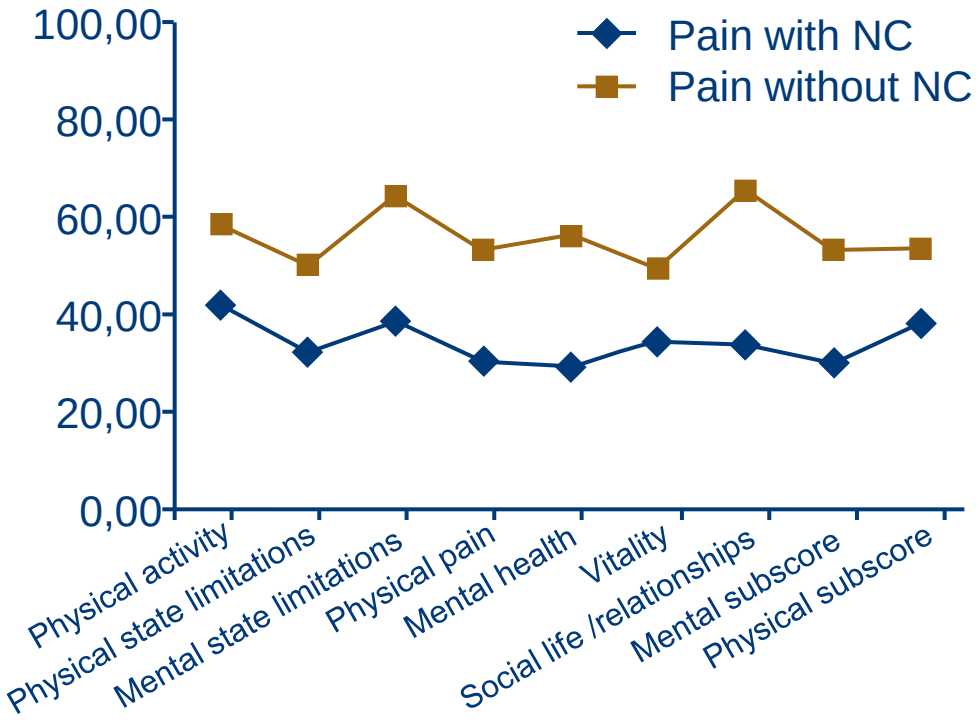
PAIN®

www.elsevier.com/locate/pain

The specific disease burden of neuropathic pain: Results of a French nationwide survey

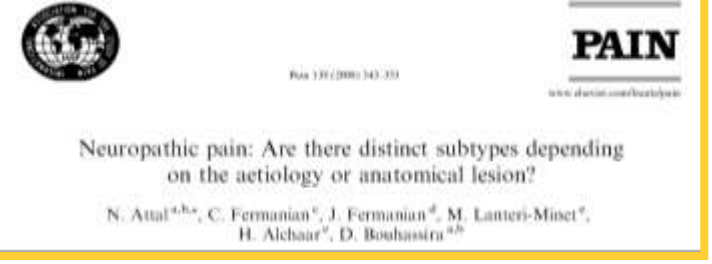
Nadine Attal[a,b,c,*], Michel Lanteri-Minet[d], Bernard Laurent[e], Jacques Fermanian[f], Didier Bouhassira[a,b,c]

Score de qualité de vie



Traitement des douleurs neuropathiques

- Traitement pharmacologique actuels
- Recommandations
- Nouvelles molécules
- Autres approches thérapeutiques


PAIN

Neuropathic pain: Are there distinct subtypes depending on the aetiology or anatomical lesion?

N. Attal, C. Fermanian, J. Fermanian, M. Lanteri-Minet, H. Alchaar, D. Bouhassira

Des symptômes qui ne dépendent pas de l'étiologie

	Zona	Diabète	Autre neuro-pathie	Trauma	Radicu-lopathie	Névral-gie du V	Trauma moelle	SEP	Syrinx	AVC
	n=49	n=35	n=53	n=110	n=43	n=18	n=25	n=32	n=40	n=31
Brulûre	89.8	62.8	58.5	51.1	65.1	16.7	76	56.2	75	74.2
Douleur profonde	28.5	68.6	62.3	58	51.2	22.2	74	62.5	60	64.5
Douleur paroxystique	63.2	62.8	62.3	66.3	72	89.9	72	65.6	65	58
Douleur provoquée	91.9	51.5	64.1	76	44.2	61.1	70	75	62.5	74
Paresthé-sies	30	82.9	84.9	86	81.4	33	80	84.4	87.5	83.9

Le traitement ne dépend pas ou peu de l'étiologie

Traitement pharmacologique des DN

Antalgiques de palier I
AINS
AD sérotoninergiques
Benzodiazépines
Neuroleptiques

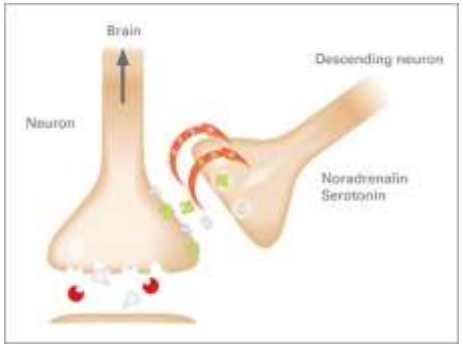
Certains antidépresseurs
Prégabaline/gabapentine
Opiacés
Topiques anesthésiques
Capsaïcine

Finnerup, Attal et al Lancet Neurol 2015

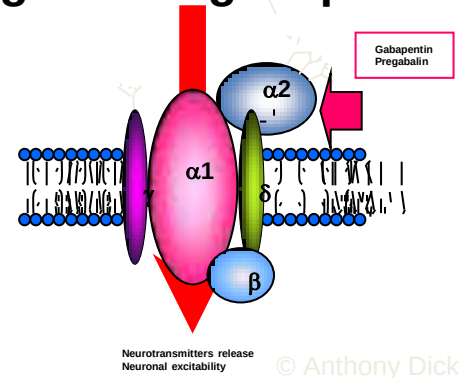
Principaux traitements médicamenteux

Finnerup, Attal et al Lancet Neurol 2015

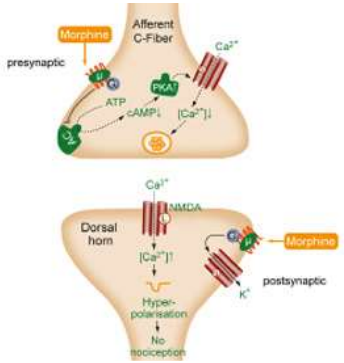
Antidépresseurs tricycliques/ISRNA (amitriptyline, duloxétine)



Antiépileptiques prégabaline/gabapentine



Opioïdes forts/tramadol/tapentadol

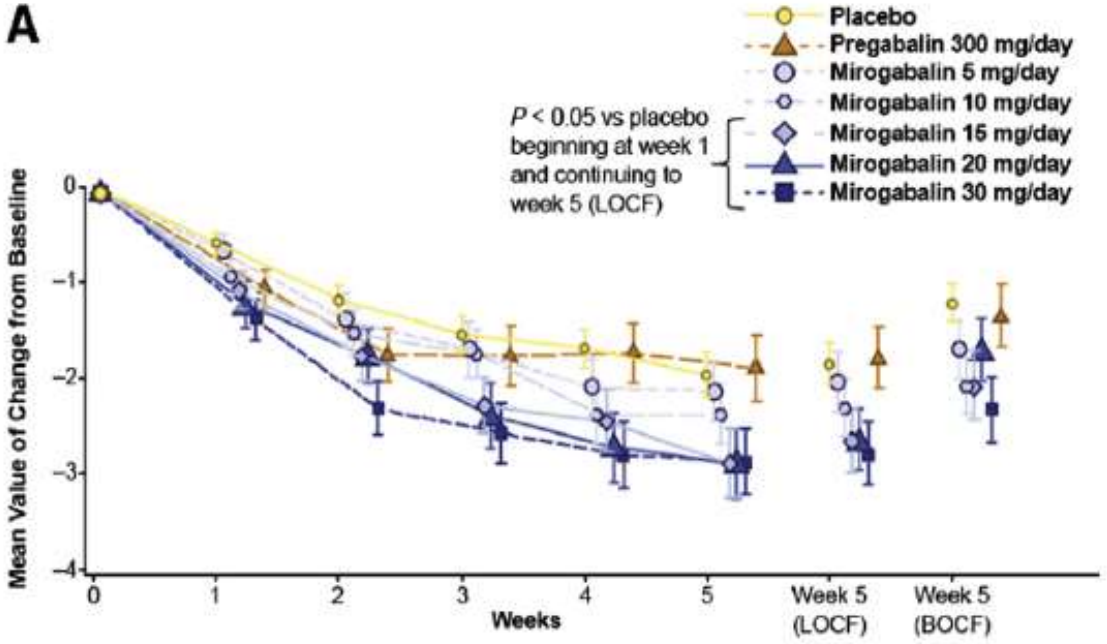


ISRNA : inhibiteurs mixtes de recapture de la sérotonine et de la noradrénaline

Efficacy and Safety of Mirogabalin (DS-5565) for the Treatment of Diabetic Peripheral Neuropathic Pain: A Randomized, Double-Blind, Placebo- and Active Comparator–Controlled, Adaptive Proof-of-Concept Phase 2 Study

Aaron Vinik,[1] Julio Rosenstock,[2] Uma Sharma,[3] Karen Feins,[4] Ching Hsu,[4] and Domenico Merante,[5] on behalf of the DS5565-A-U201 US Phase II Study Investigators

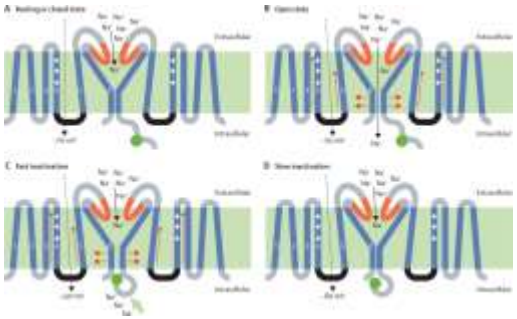
Diabetes Care 2014;37:3253–3261 | DOI: 10.2337/dc14-1044



Traitements topiques/locaux

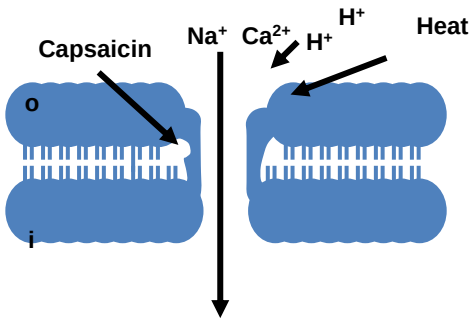
Lidocaine 5% (patches)

Effets sur canaux sodiques



Capsaïcine

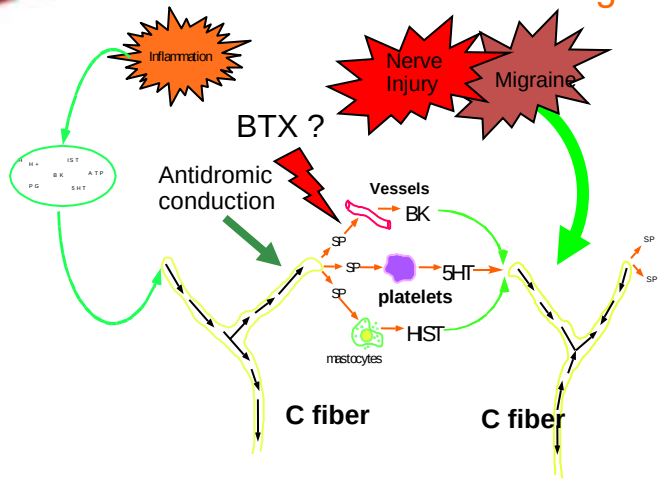
Agoniste TRPV1



Tominaga & Julius 2001

Toxine botulinique A

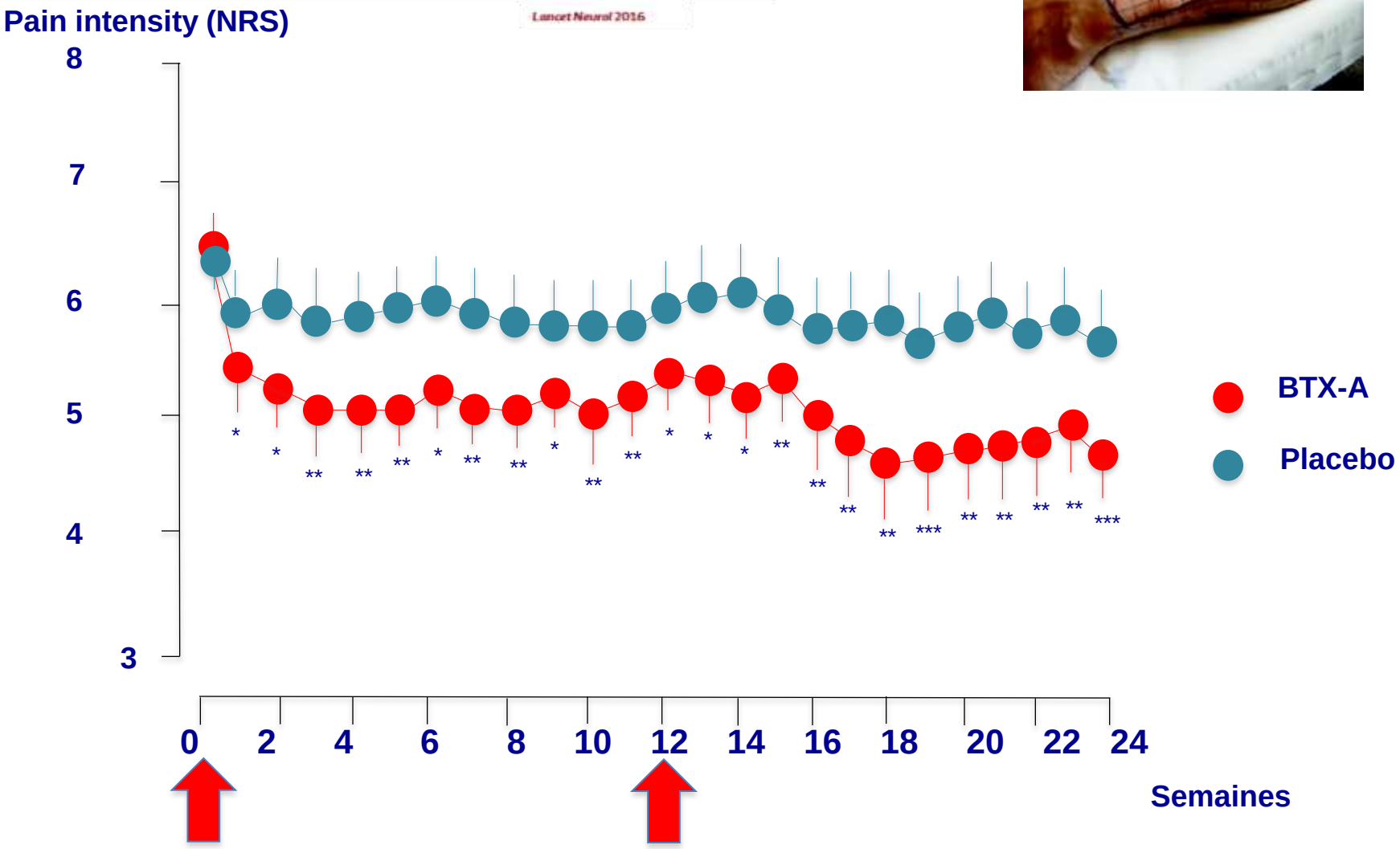
Effet sur l'inflammation neurogène?.



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



Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Nanna B Finnerup*, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace

Lancet Neurol 2015

GRADE

Douleur neuropathique

Strong for

- Pregabaline
- Gabapentine
- Antidépresseus tricycliques
- Antidépresseurs ISRNA

Weak for

- Tramadol
- Pour la DN périphérique :
  - Patches lidocaine
  - Patches de capsaIcine 8 %

Weak for

- Opiacés forts
- Toxine botulinique A

Problèmes posés par ces recommandations

- Pas de recommandation sur les combinaisons
- Les molécules proposées en première intention sont faiblement efficaces
- Certaines molécules non recommandées sont probablement efficaces

Attal and Bouhassira Pain 2019

PAIN® 154 (2013) 2616–2625

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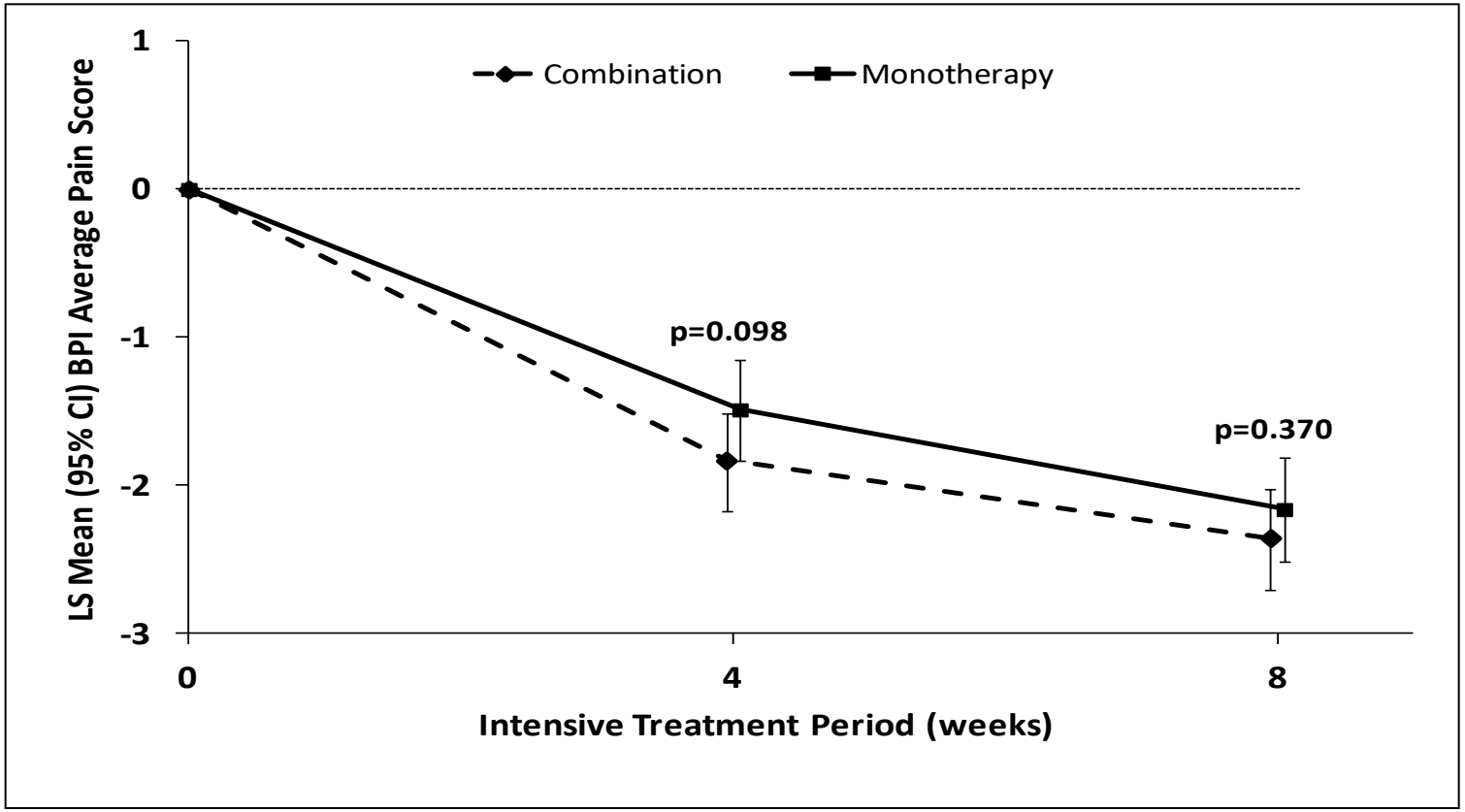
Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain

Solomon Tesfaye [a,*], Stefan Wilhelm [b], Alberto Lledo [c], Alexander Schacht [d], Thomas Tölle [e], Didier Bouhassira [f], Giorgio Cruccu [g], Vladimir Skljarevski [h], Rainer Freynhagen [i]



PAIN® 154 (2013) 2616–2625

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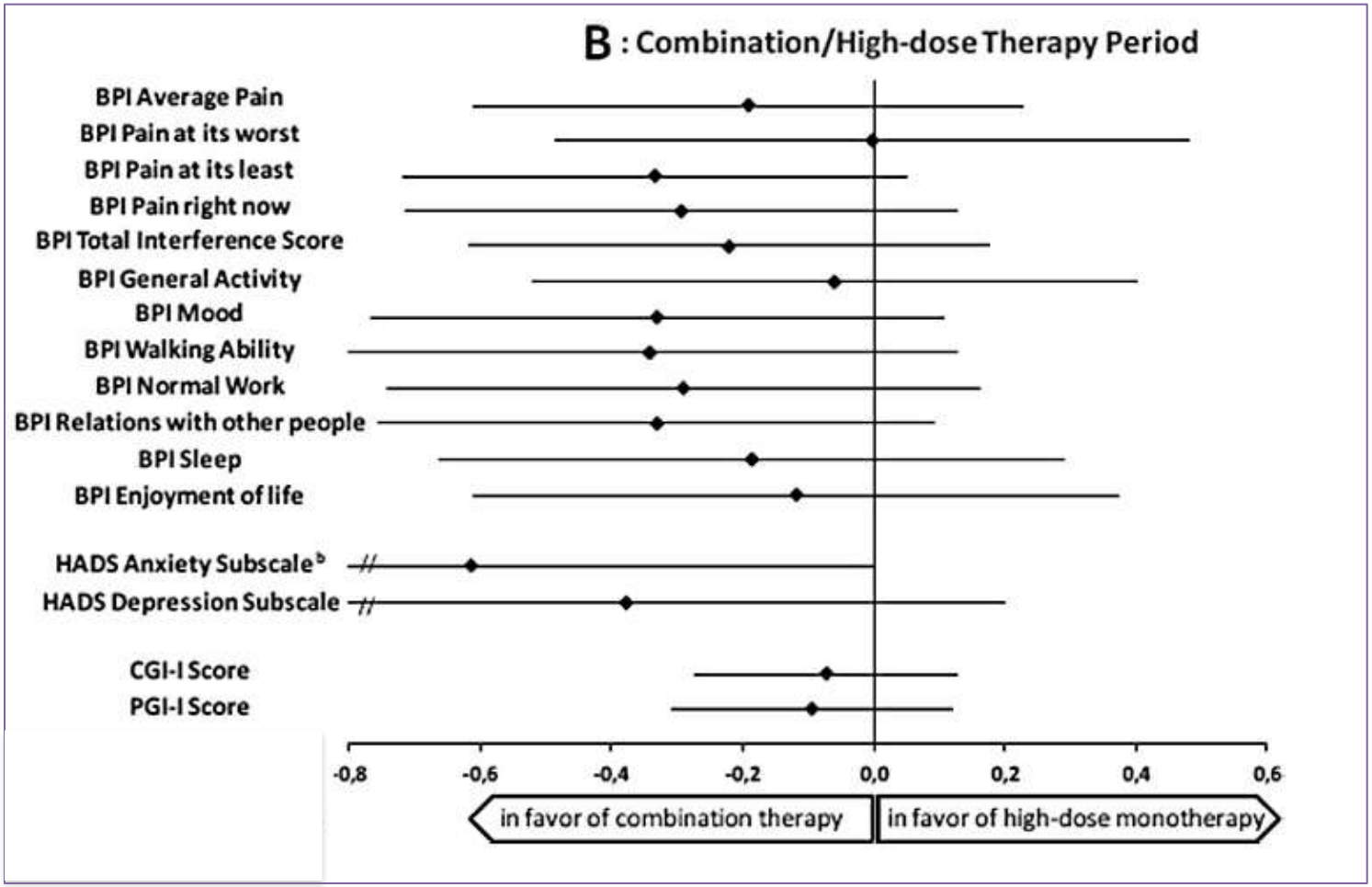


Etudes de combinaisons

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Ian Gilron, M.D., Joan M. Bailey, R.N., M.Ed., Dongsheng Tu, Ph.D., Ronald R. Holden, Ph.D., Donald F. Weaver, M.D., Ph.D., and Robyn L. Houlden, M.D.

Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial

Ian Gilron, Joan M Bailey, Dongsheng Tu, Ronald R Holden, Alan C Jackson, Robyn L Houlden

Research Paper

PAIN

Combination of morphine with nortriptyline for neuropathic pain

Ian Gilron[a,*], Dongsheng Tu[b], Ronald R. Holden[c], Alan C. Jackson[d], Deborah DuMerton-Shore[e]

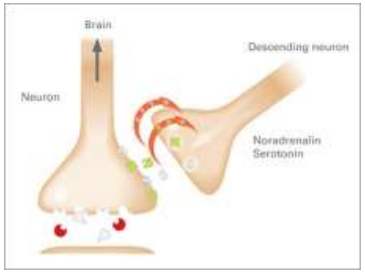
Research Paper

PAIN

Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial

Jakob V. Holbech[a,*], Flemming W. Bach[b], Nanna B. Finnerup[c], Kim Brøsen[d], Troels S. Jensen[c], Søren H. Sindrup[a]

Méta-analyse : antidépresseurs ISRNA



SNRIs NNT meta-analysis forest plot (fixed effects)

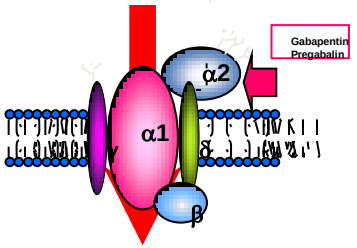
Pain condition	Drug Doses	Reference	NNT (95% CI)
PPN	Venlafaxine 225 mg	Sindrup et al. 2003a	5.1 (2.6-68.8)
PPN	Venlafaxine 150, 225 mg	Rowbotham et al. 2004	4.5 (2.7-13.5)
PPN	Duloxetine 60,120 mg	Goldstein et al. 2005	4.2 (2.9-7.2)
PPN	Duloxetine 60, 120 mg	Raskin et al. 2005	7.0 (4.0-27.0)
PPN	Duloxetine 60, 120 mg	Wernicke et al. 2006	4.8 (3.2-9.7)
PPN	Duloxetine 120 mg	Gao et al. 2010	30.2 (6.0- -10.0)
PPN	Duloxetine 40, 60 mg	Yasuda et al. 2011	5.2 (3.5-10.1)
PPN	Duloxetine 60 mg	Rowbotham et al. 2012	6.1 (2.9- -48.5)
MS	Duloxetine 60 mg	NCT00755807/Vollmer et al. 2013	15.1 (6.0- -29.0)
PPN	Desvenlafaxine 50-400 mg	NCT00283842	10.4 (5.0- -109)
Combined (fixed effects)			6.4 (5.2-8.4)

5 10 ∞ 10 5 3.3 2.5 2

NNT (harm) **NNT (benefit)**

Finnerup, Attal et al 2016

Méta-analyse : prégabaline



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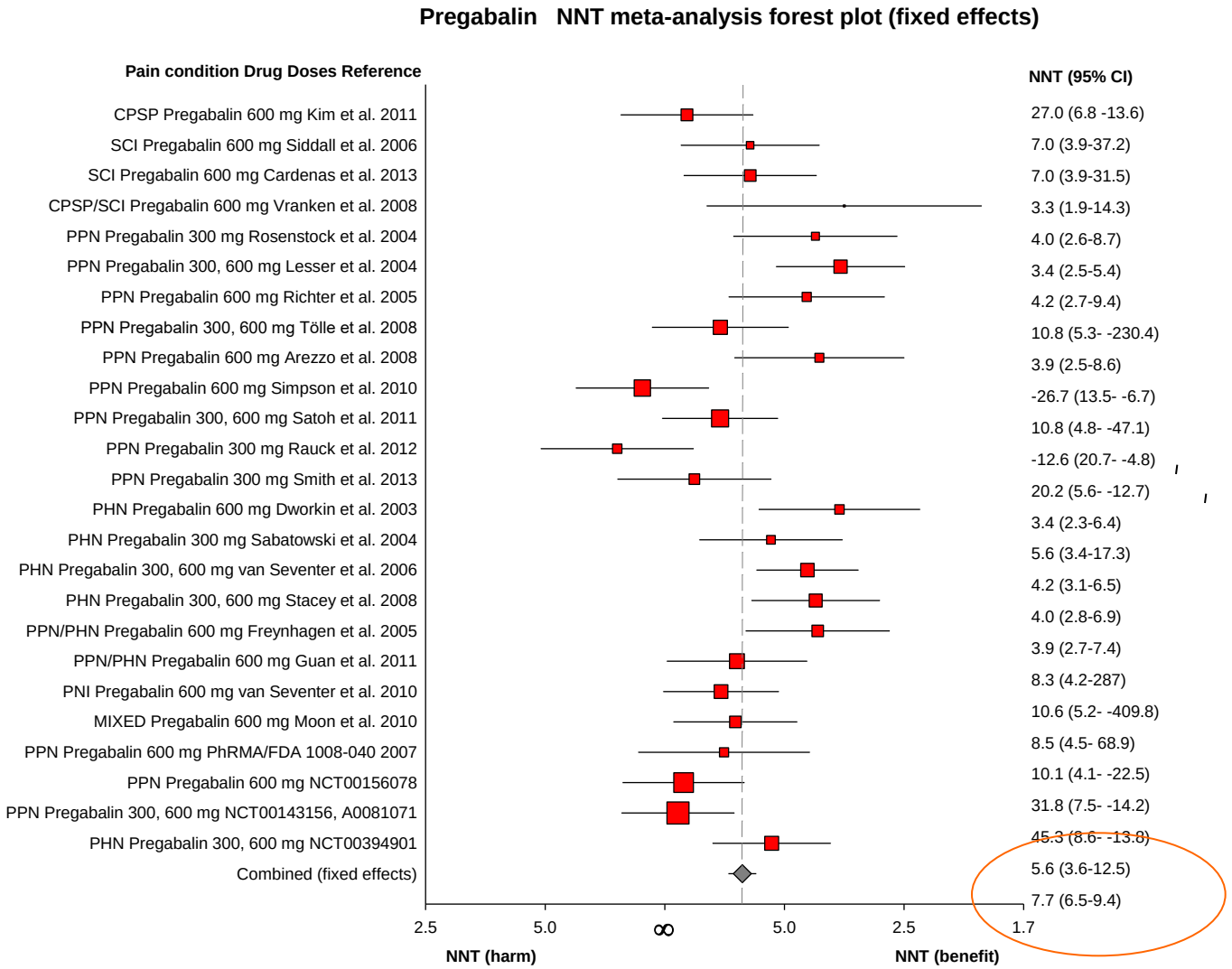
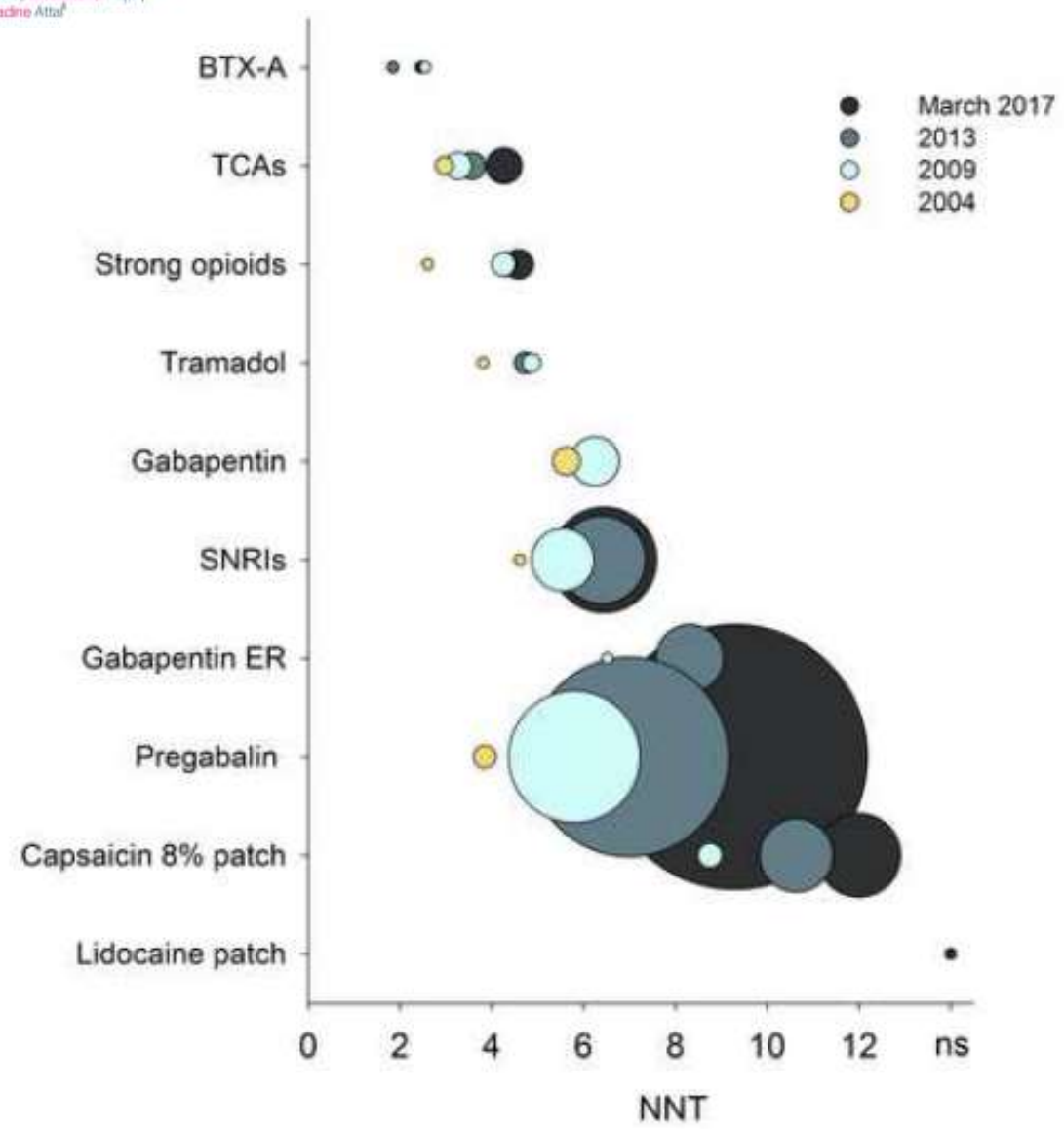


Research Paper
PAIN

Neuropathic pain clinical trials: factors associated with decreases in estimated drug efficacy

Nanna B. Finnerup[a,b,*], Simon Haroutounian[c], Ralf Baron[d], Robert H. Dworkin[e,f,g], Ian Gilron[h], Maija Haanpää[i], Troels S. Jensen[a,b], Peter R. Kamerman[j,k], Ewan McNicol[l,m], Andrew Moore[n], Srinivasa N. Raja[o], Niels T. Andersen[p], Emily S. Sena[q], Blair H. Smith[r], Andrew S.C. Rice[s], Nadine Attal[t]



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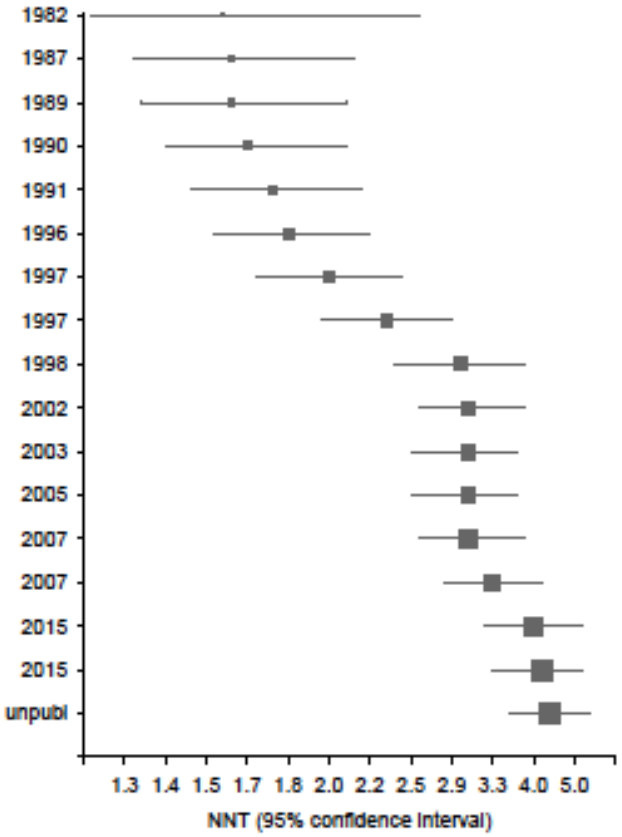
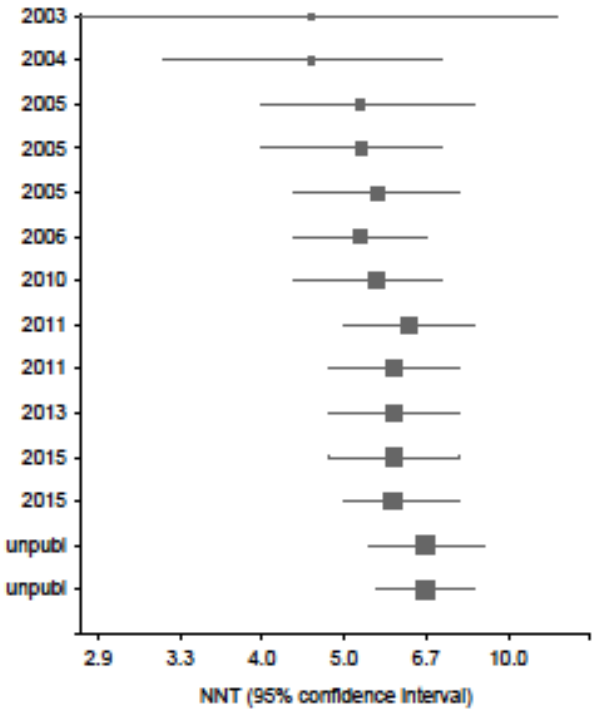
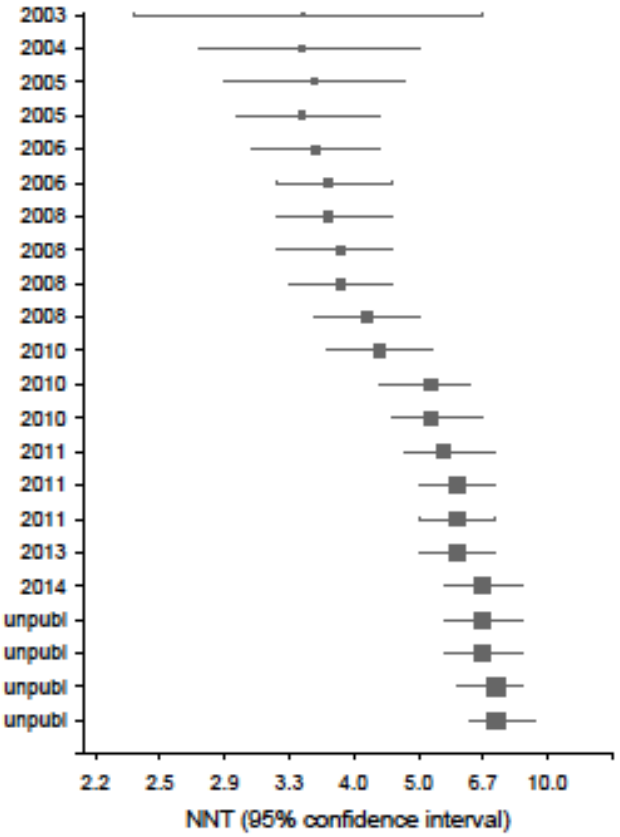
TCA



SNRI



Pregabalin 600 mg



Le cas prégabaline

Authors	Doses (mg)	Durée	Condition	N	Design	Résultat prega.
Raskin 2014	300	13	Diabète	295	Enrichie	NS
Gonzales 2015	300	4	Prediabetic	36	Enrichie	+
Raskin 2016	150-300	7	Diabète	147	Crossover	NS
Huffman 2015	300	6	Diabète	203	Crossover	NS
Mu 2018	300	8	Diabète	623	Gr parallèles	0.059
Liu 2017	300	8	Zona	349	Gr parallèles	+
Markman 2018	150-600	15	Trauma	542	Gr parallèles	NS
Holbech 2015	300	5	Polyneurop.	73	Crossover	NS
Vinik 2014	300	5	Diabète	452	Gr parallèles	NS
Smith 2014	300	15	Diabète	286	Gr parallèles	NS

In preparation

DPNP : diabetic painful neuropathic pain ; PHN : postherpetic neuralgia : PN : polyneuropathy

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Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain

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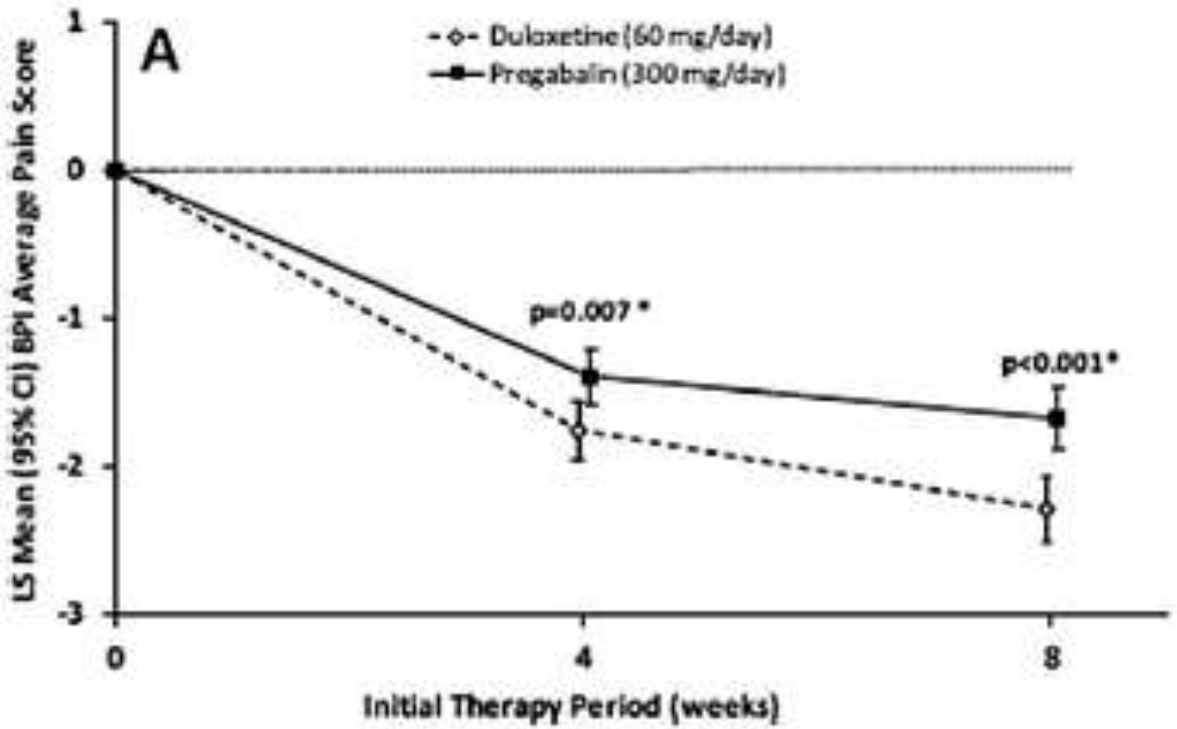
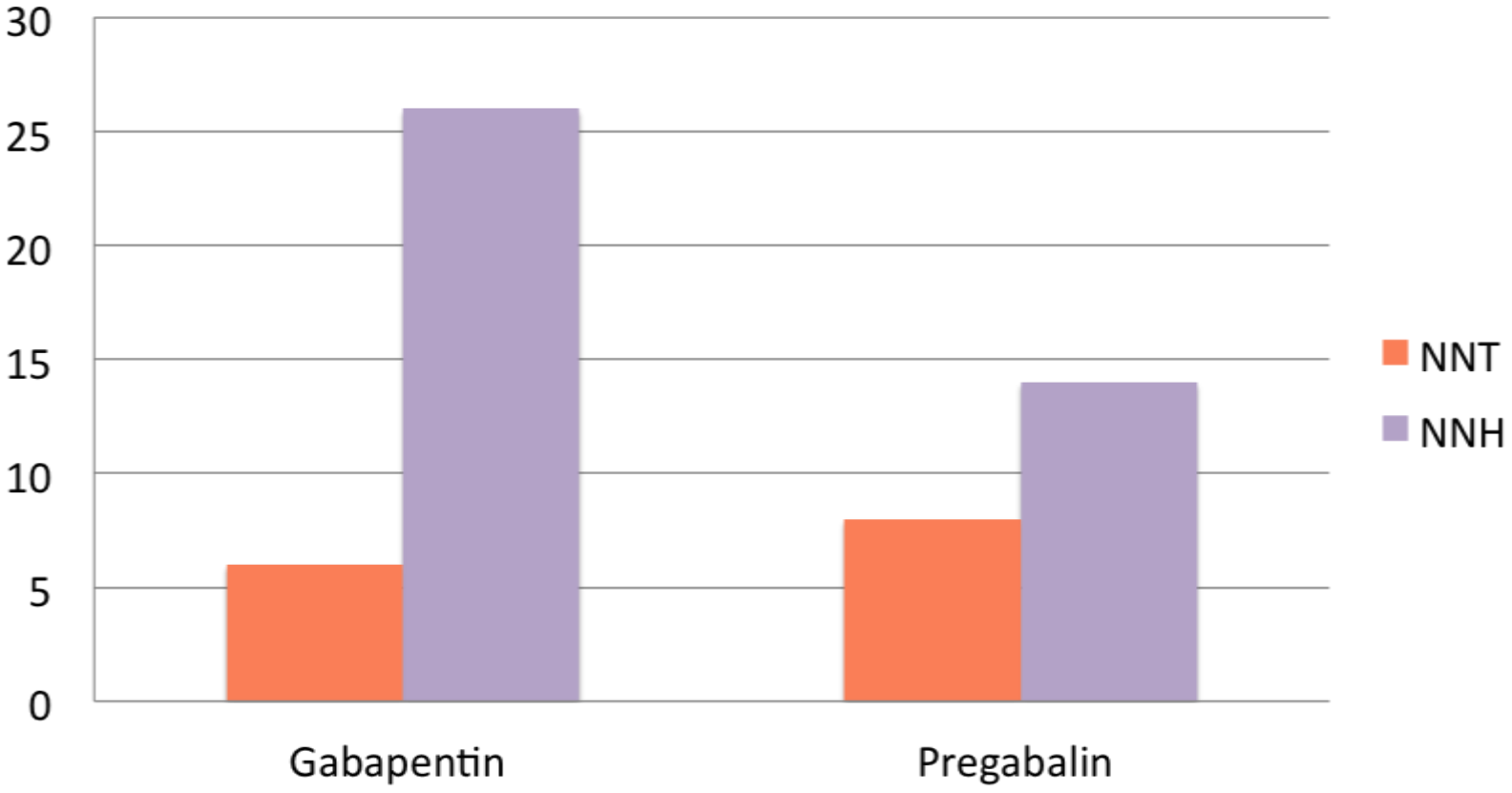


Répondeurs 30 % efficacité: 52 % duloxétine versus 37 % prégabaline ($p < 0.001$)

Prégabaline vs gabapentine



Finnerup, Attal et al Lancet Neurol 2015

Prégabaline vs gabapentine
Une étude comparative dans la sciatique

Head to Head		
VAS, difference		
GBP	1.72 (1.17)	.035
PGB	0.94 (1.09)	
ODI, difference		
GBP	10.66 (9.90)	.63
PGB	8.78 (8.86)	

Robertson et al JAMA Neurol 2019

Prégabaline vs gabapentine

Table 3. Adverse Events Experienced by Population[a,b,c]

Description	Prevalence, No. (%)	Population With Adverse Event, %
Pregabalin (n = 31)		
Nausea, vomiting, headache	7 (22.6)	39
Bowel disturbance	5 (16.1)	28
Diplopia, dysarthria	5 (16.1)	28
Dizziness, vertigo	4 (12.9)	23
Drowsy, sedation	3 (9.7)	17
Lethargy, numbness	2 (6.5)	11
Dry mouth	1 (3.2)	6
Alertness		
Weight gain		
Erectile dysfunc		
Psychiatric disturbance	1 (3.2)	6
Gabapentin (n = 7)		
Drowsy, sedation	3 (42.9)	17
Dizziness, vertigo	2 (28.6)	11
Nausea, vomiting, headache	1 (14.3)	6
Alertness	1 (14.3)	6

81 % versus 19 %
P = 0.002

Robertson et al JAMA Neurol 2019

Les molécules non recommandées semblent efficaces sur des sous groupes

European Journal of Pain 15 (2011) 441–443

Contents lists available at ScienceDirect

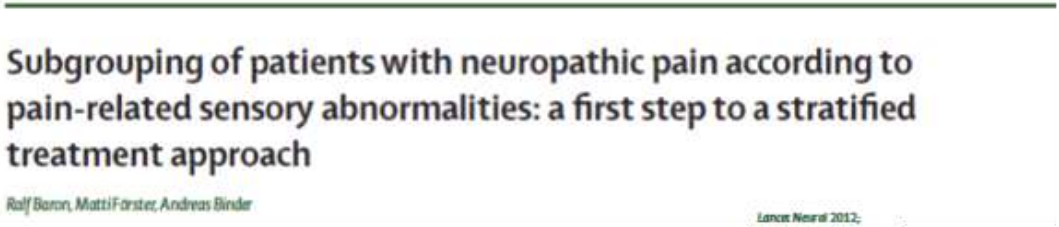
European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Editorial

Assessing symptom profiles in neuropathic pain clinical trials: Can it improve

Attal, Bouhassira, Baron, Dostrovsky et al



Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach

Ralf Baron, Matti Forster, Andreas Binder

Lancet Neurol 2012; 11: 999-1005

Deconstructing the Neuropathic Pain Phenotype to Reveal Neural Mechanisms

Christian A. von Hehn,[1,2] Ralf Baron,[3] and Clifford J. Woolf[1,2,*]

[1]FM Kirby Neurobiology Center, Children's Hospital Boston, Boston, MA 02115, USA

[2]Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA

[3]Division of Neurological Pain Research and Therapy, Department of Neurology, Universitätsklinikum Schleswig-Holstein, 24105 Kiel, Germany

*Correspondence: clifford.woolf@childrens.harvard.edu

DOI 10.1016/j.neuron.2012.02.008

Neuron

Review

Reappraising neuropathic pain in humans —how symptoms help disclose mechanisms

Andrea Truini, Luis García-Larrea and Giorgio Cruccu

NATURE REVIEWS | NEUROLOGY VOLUME 9 | OCTOBER 2013

Voir aussi Bouhassira and Attal Neurosciences 2016 ; Attal and Bouhassira Pain 2019; Colloca et al Nat. Dis Primers 2017 ; Attal, Baron, Bouhassira Lancet Neurol 2018

PAIN® 155 (2014) 2263–2273

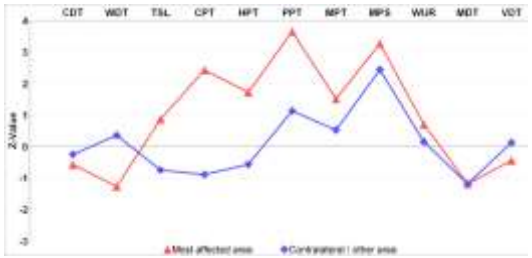
PAIN®

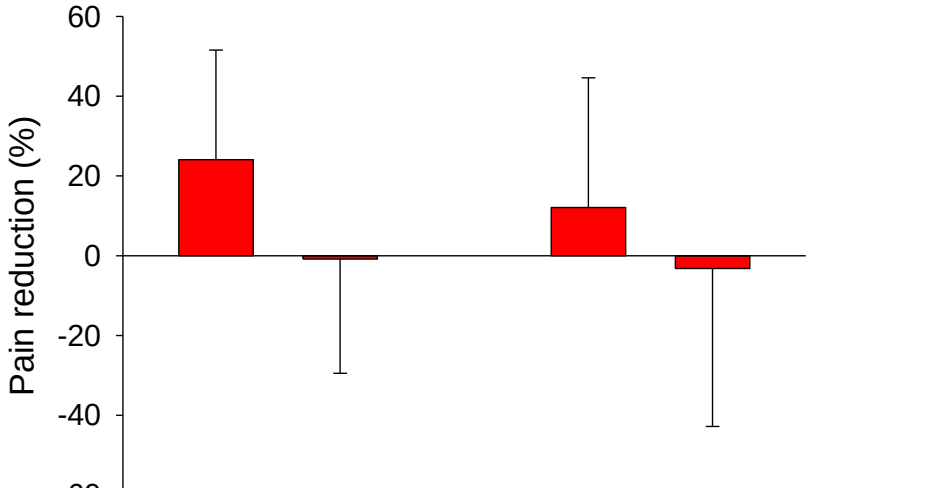
www.elsevier.com/locate/pain

The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study

Dyveke T. Demant [a], Karen Lund [b], Jan Vollert [c], Christoph Maier [c], Märtha Segerdahl [d,e], Nanna B. Finnerup [b], Troels S. Jensen [b], Søren H. Sindrup [a,*]

Tests quantifiés sensoriels





NPSI

Patients ayant brulûre et décharges électriques
Meilleurs répondeurs

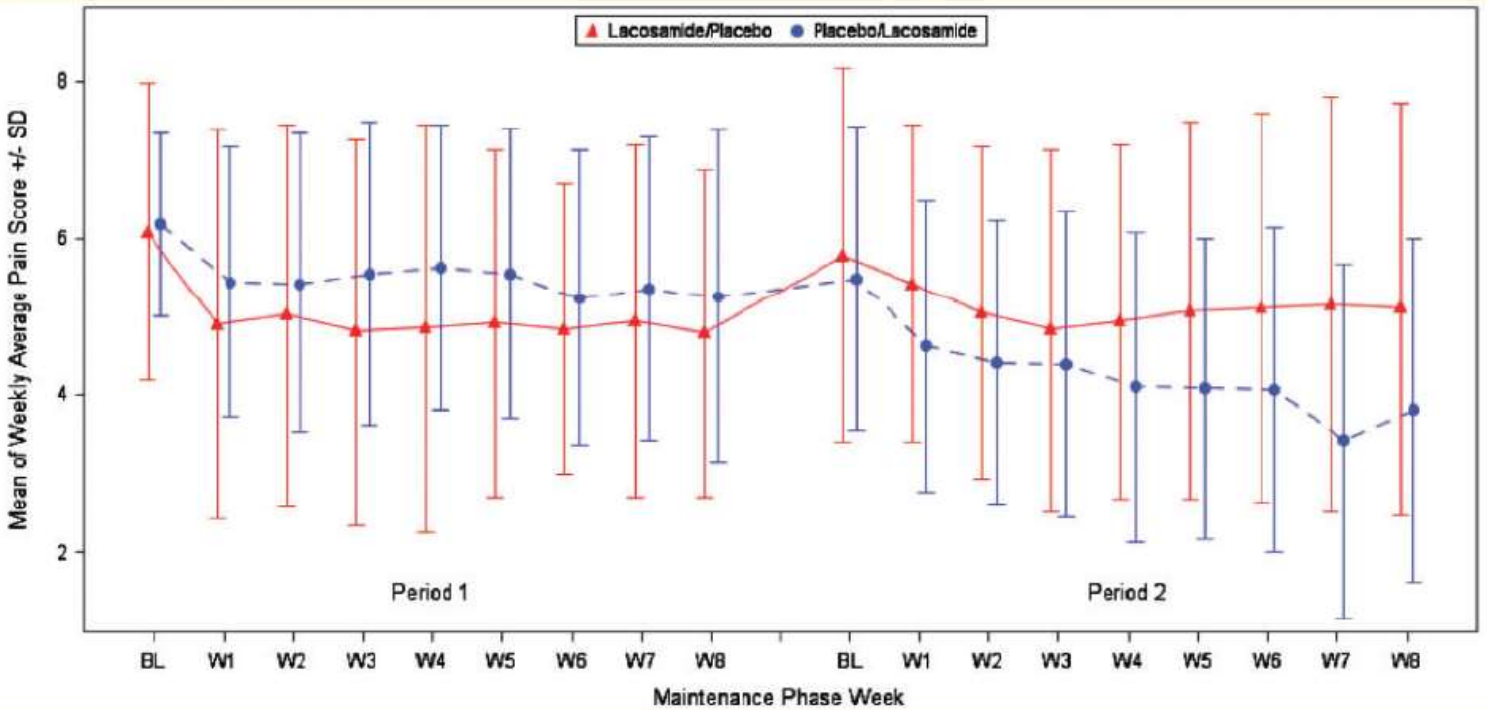
doi:10.1093/brain/awy329 BRAIN 2019: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

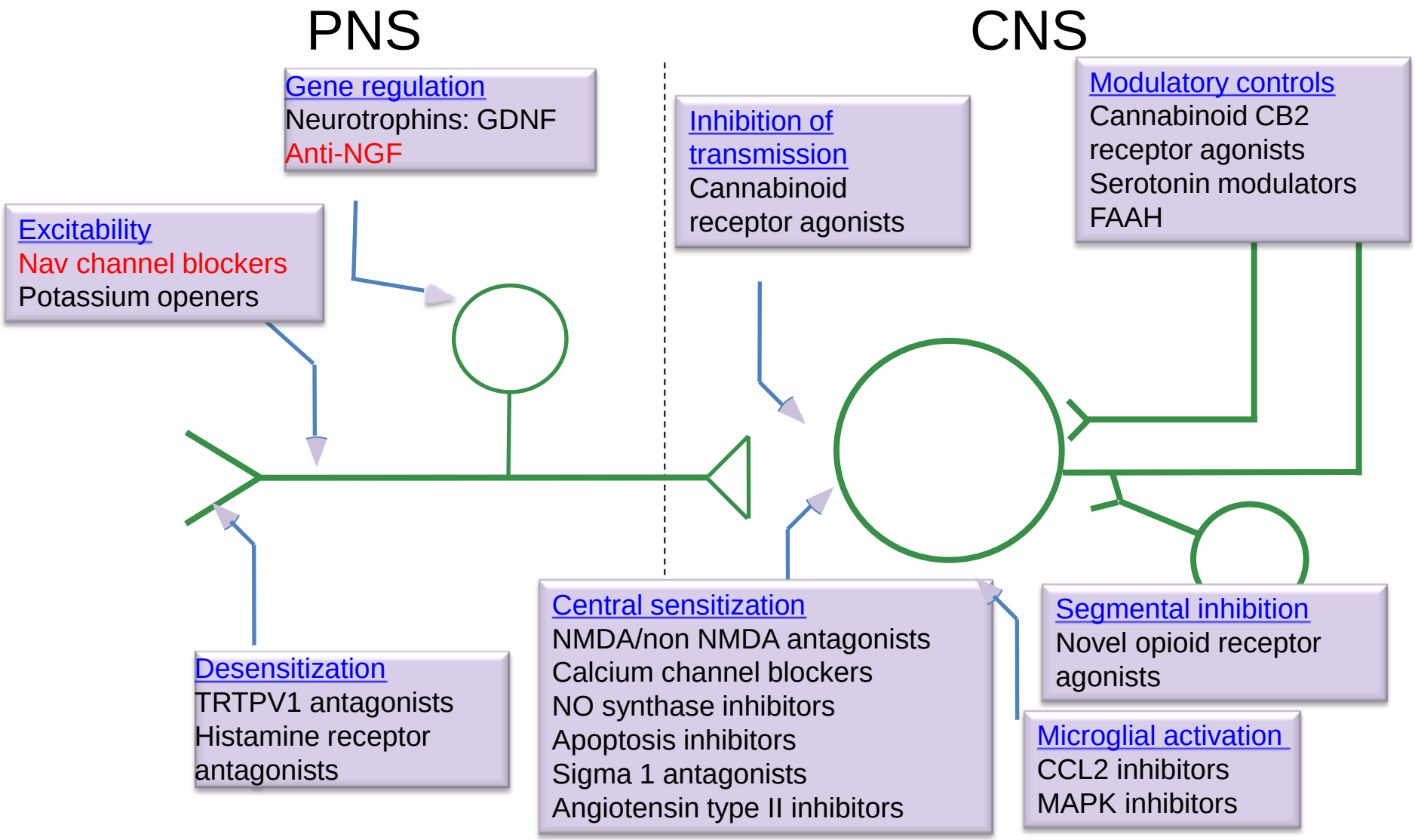
CLINICAL TRIAL

Lacosamide in patients with $Na_v1.7$ mutations-related small fibre neuropathy: a randomized controlled trial

Bianca T.A. de Greef,[1] Janneke G.J. Hoeijmakers,[1] Margot Geerts,[1] Mike Oakes,[2] Tim J.E. Church,[3] Stephen G. Waxman,[4,5] Sulayman D. Dib-Hajj,[4,5] Catharina G. Faber[1] and Ingemar S.J. Merkies[1,6]



Nouvelles cibles pharmacologiques



Gilron and Dickenson 2014 ; Attal and Bouhassira 2019

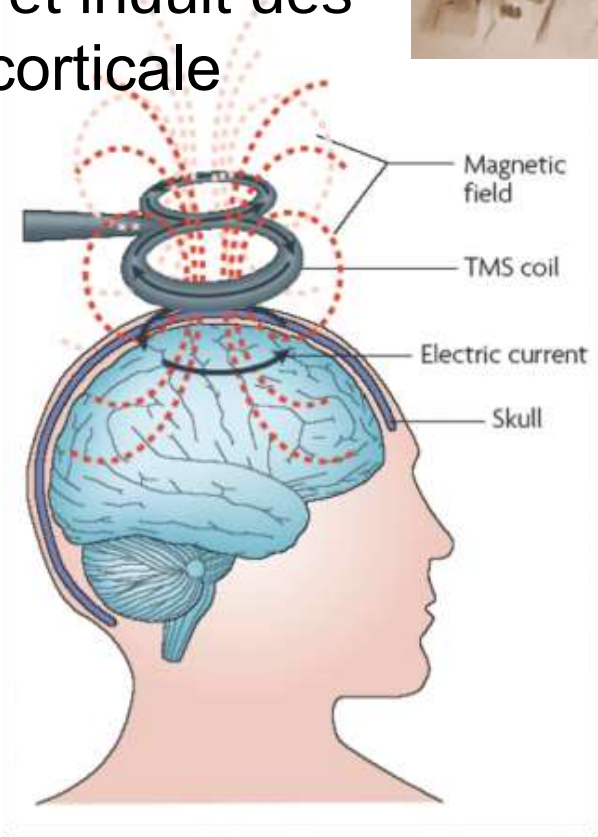
Autres traitements

- Techniques de neurostimulation périphériques (TENS) et centrale invasive et non invasive

- Autres approches : hypnose, relaxation, TCC, biofeedback, rééducation, éducation thérapeutique : peu d'études spécifiques

Stimulation magnétique transcrânienne : une technique de stimulation cérébrale non invasive

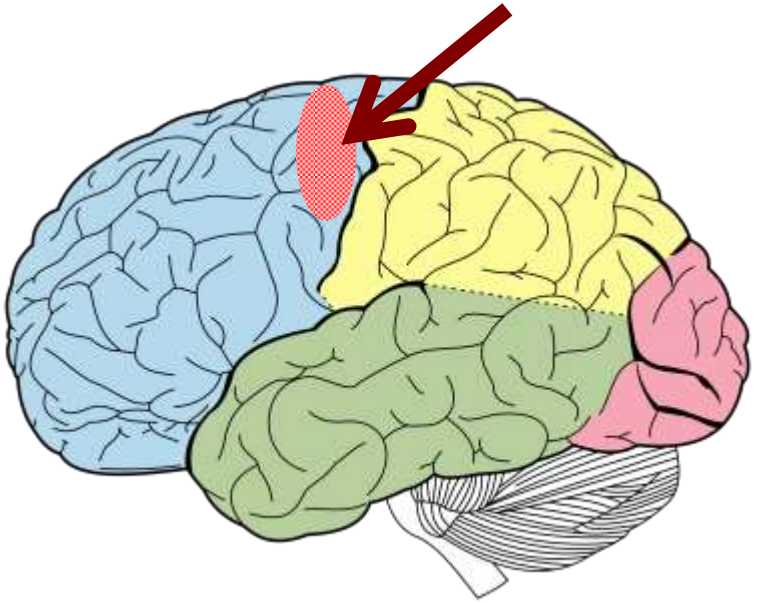
- Basée sur le principe de l'induction életromagnétique (Faraday, 1831)
- Active des circuits neuronaux et induit des modifications de l'excitabilité corticale



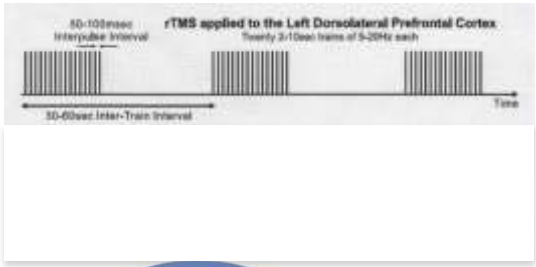
Paramètres de stimulation conventionnels de la rTMS en analgésie

- Aires de stimulation

Cortex moteur primaire



- Fréquence de stimulation: 5-20 Hz
- Intensité of stimulation : 80 % du seuil moteur
- Bobine en forme de « huit »

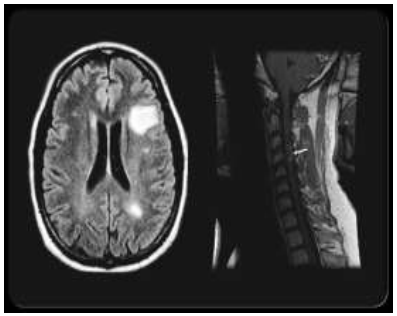


Deux grandes indications cliniques en analgésie

Douleur neuropathique

Douleur post-zostérienne

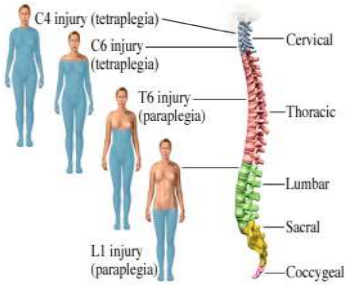
DN postsurgicale



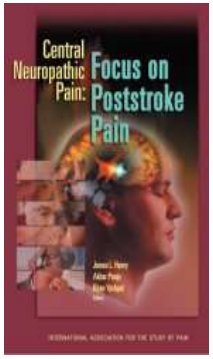
SEP

Polyneuropathyie

DI radiculaire

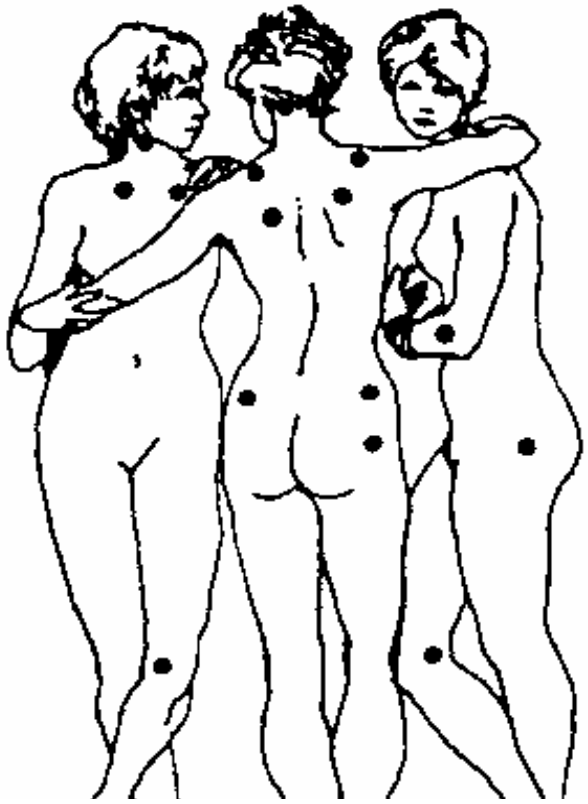


Lésion médullaire



AVC

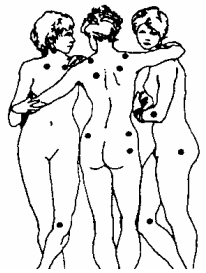
Fibromyalgie



doi:10.1093/brain/awm189 Brain (2007), 130, 2661–2670

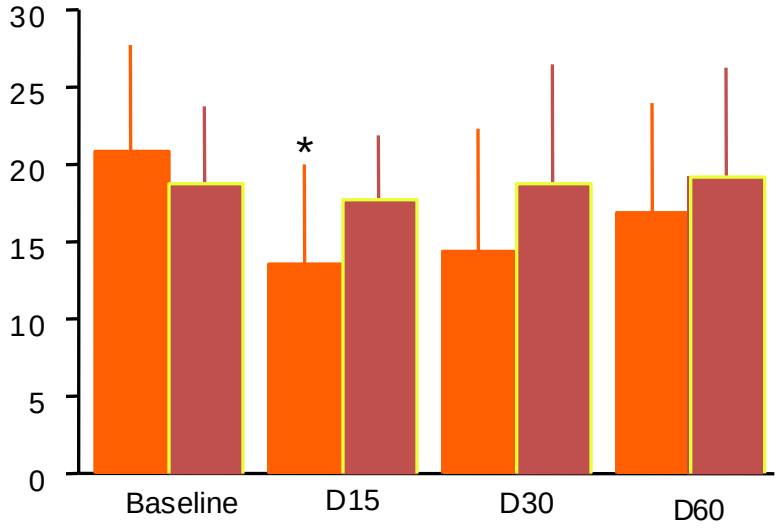
Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia

A. Passard,[1] N. Attal,[1] R. Benadhira,[2] L. Brasseur,[1] G. Saba,[2] P. Sichere,[3] S. Perrot,[4] D. Januel[2] and D. Bouhassira[1]

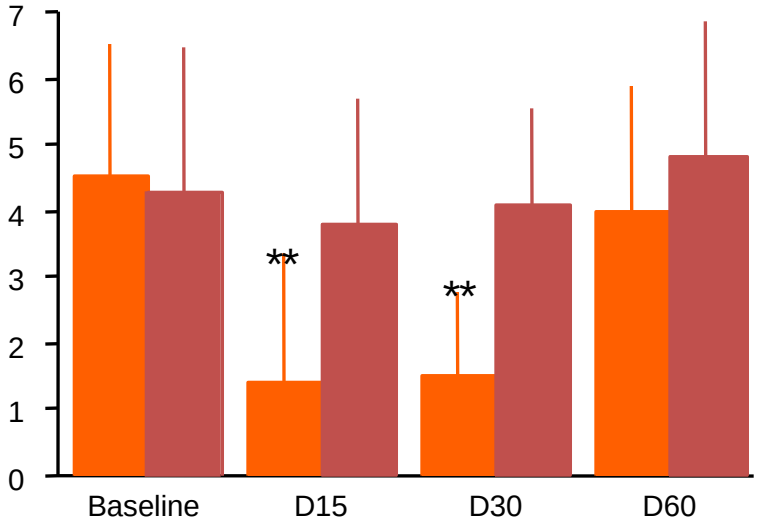


Meilleurs effet sur la composante affective de la douleur

Score sensoriel*



Score affectif*



* Questionnaire abrégé de McGill

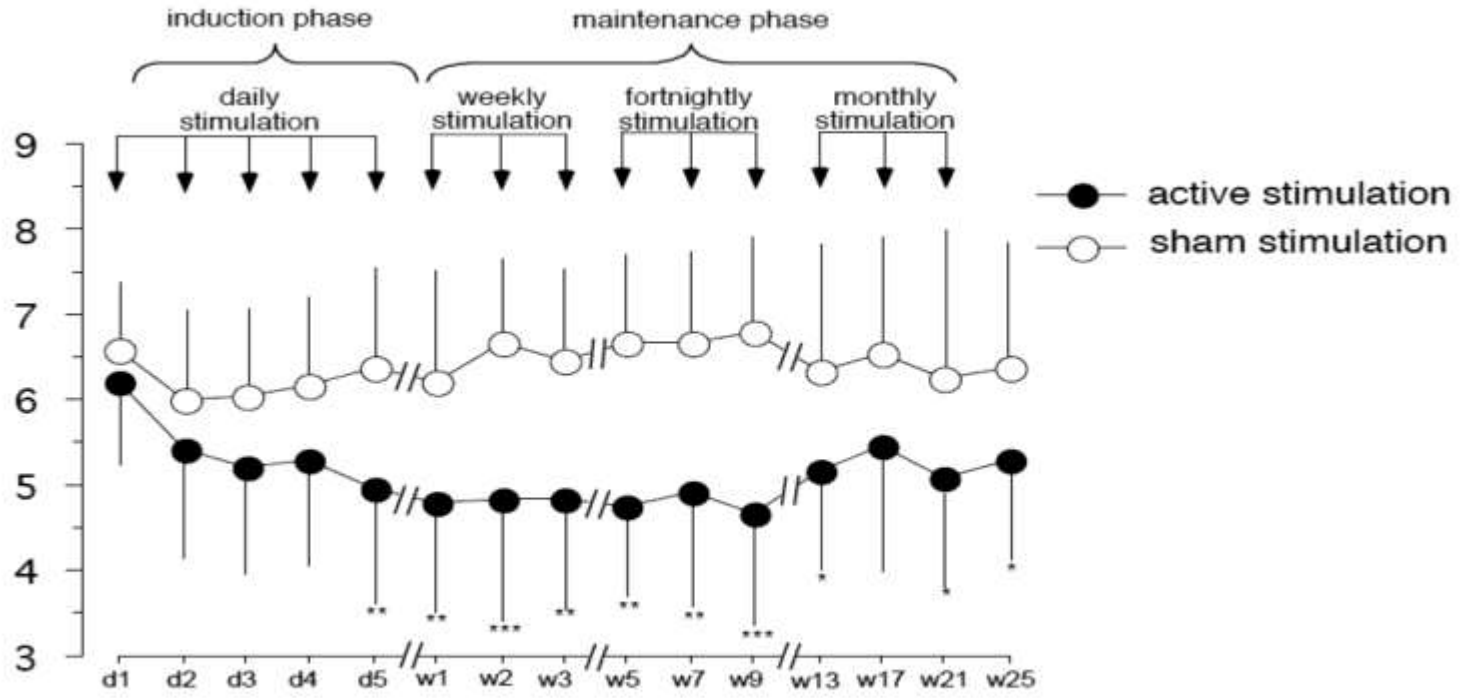
PAIN® 152 (2011) 1478–1485

PAIN®

Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia

Alaa Mhalla [a,1], Sophie Baudic [a,1], Daniel Ciampi de Andrade [b], Michele Gautron [a], Serge Perrot [a,c,d], Manoel Jacobsen Teixeira [b], Nadine Attal [a], Didier Bouhassira [a,e]

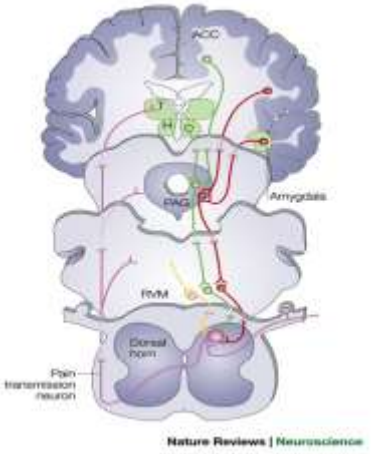
Maintien de l'efficacité au cours du temps après stimulations répétées sur 6 mois



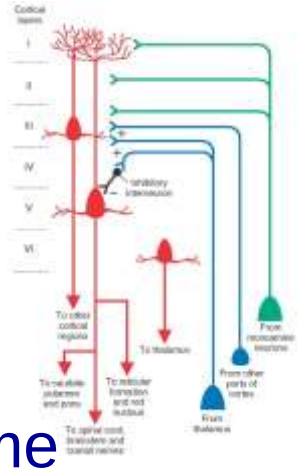
Mécanismes potentiels de l'effet analgésique

Plusieurs hypothèses

Mise en jeu des systèmes modulateurs de la douleur



Modifications de l'excitabilité corticale



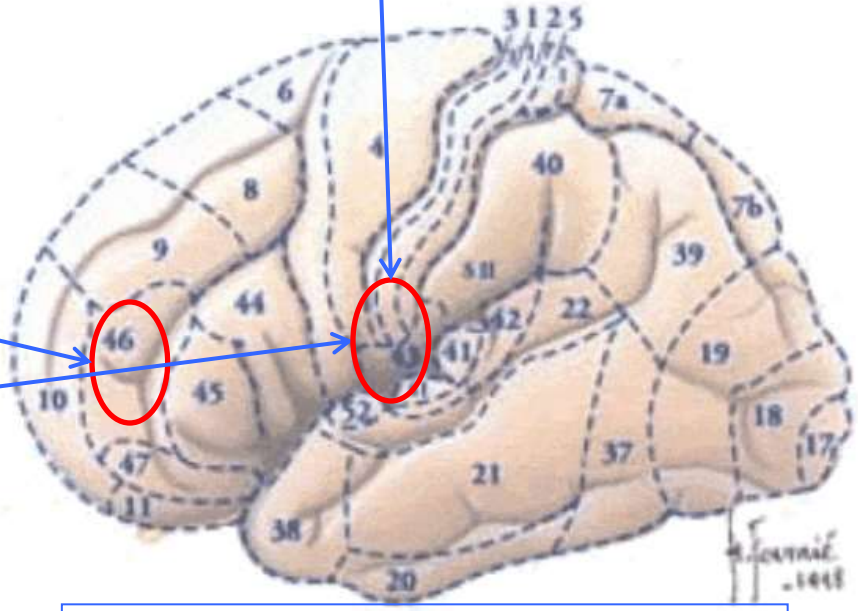
Modifications à long terme de la plasticité cérébrale

Moisset et al E J Pain 2016

Nouveaux paramètres de stimulation

Stimulation thêta burst

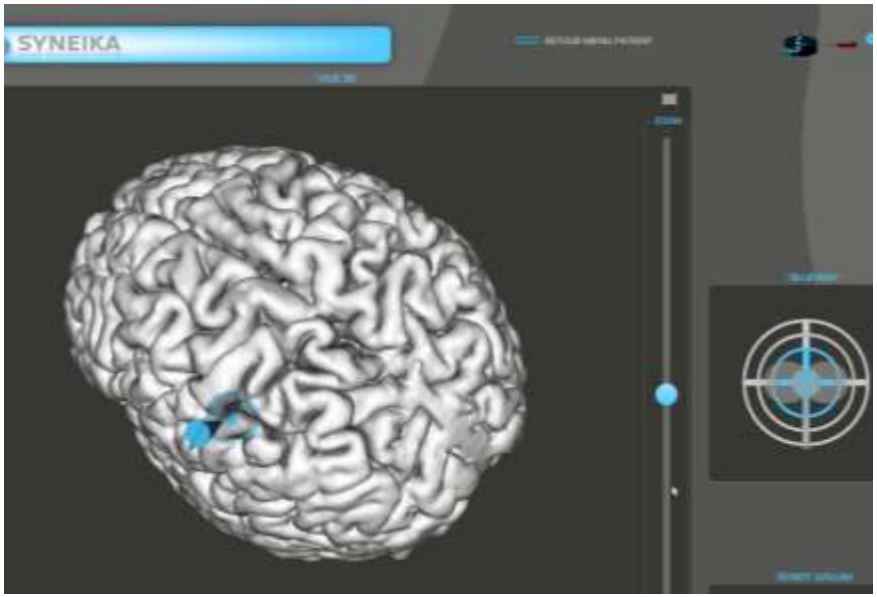
Stimulation d'autres aires corticales (cortex préfrontal)



rTMS « profonde » par courants Hesed Coil

Développements technologiques

Sonde double face (active/placebo)



Neuronavigation haute précision assistée d'un robot

Perspectives

- Les recommandations en matière de douleur neuropathique vont prochainement être actualisées

- Pour la première fois, elles vont intégrer l'ensemble des traitements pharmacologiques et non pharmacologiques