Diabetic neuropathic pain : new symptomatic treatment options

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Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

UNIVERSITÉ VERSAILLES SAINT-QUENTIN

Conflicts of interest

- Dr Attal received honoraria by Lilly, Pfizer, Eisai, Grunenthal, Adir, Astra Zeneca and Astellas for participation to advisory board or clinical trials

Diabetic neuropathy

- **1st cause of neuropathy in Western countries**
- **Prevalence of pain : 16-26 %**

(Bouhassira et al Plos One 2013; Davies et al Diabetes Care 1996)

- **Clinical presentations**

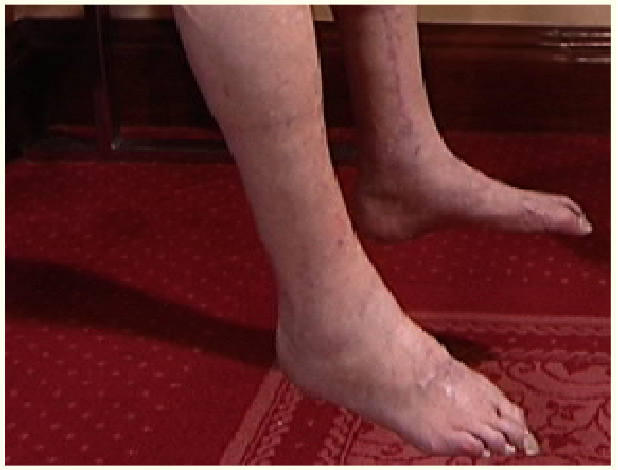
- **Mononeuropathies**
- **Dysautonomic neuropathy**
- **Polyneuropathy**

Acute

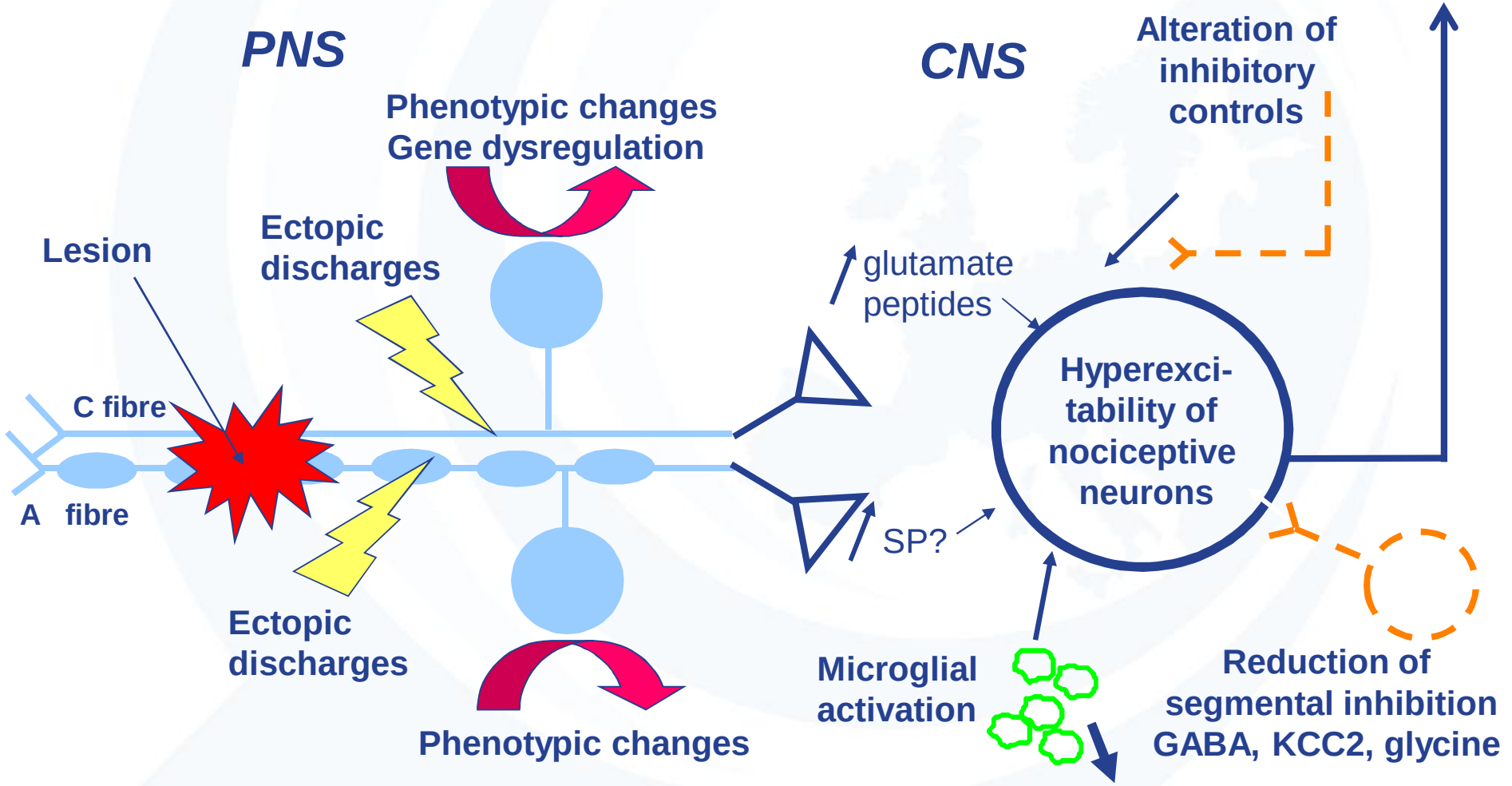
Sensitive distal chronic neuropathy

80 % of all diabetic neuropathies

(Dyck et al, Neurology 199)3

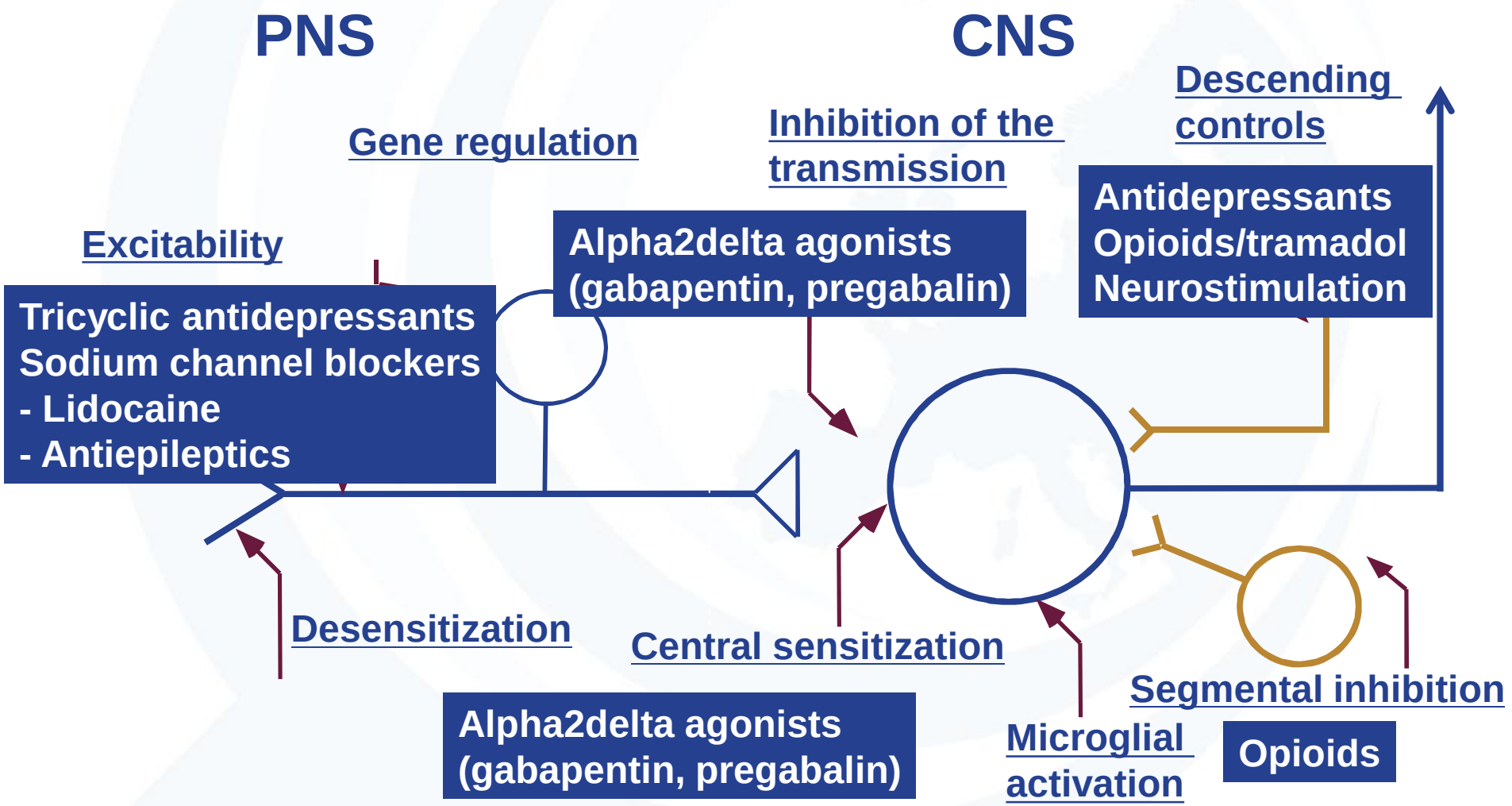


NP in diabetic neuropathy



In: Bouhassira and Attal, douleurs neuropathiques, 2007

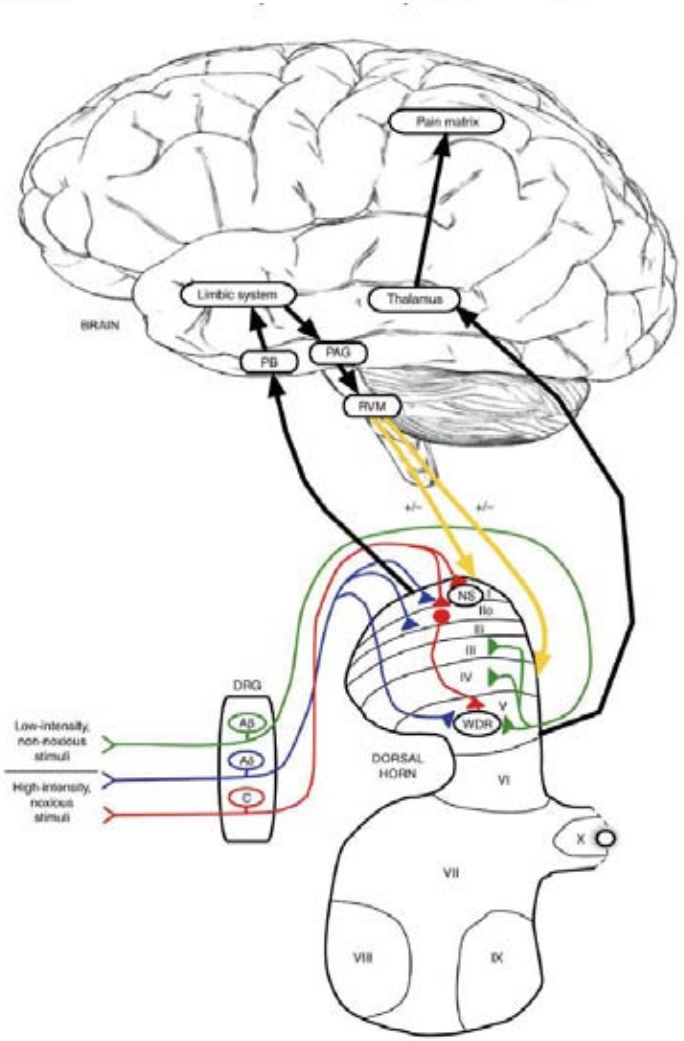
Current therapeutic targets



Antidepressants and modulatory controls

Tricyclic antidepressants (amitriptyline)

Serotonin and norepinephrine reuptake inhibitors (duloxetine)



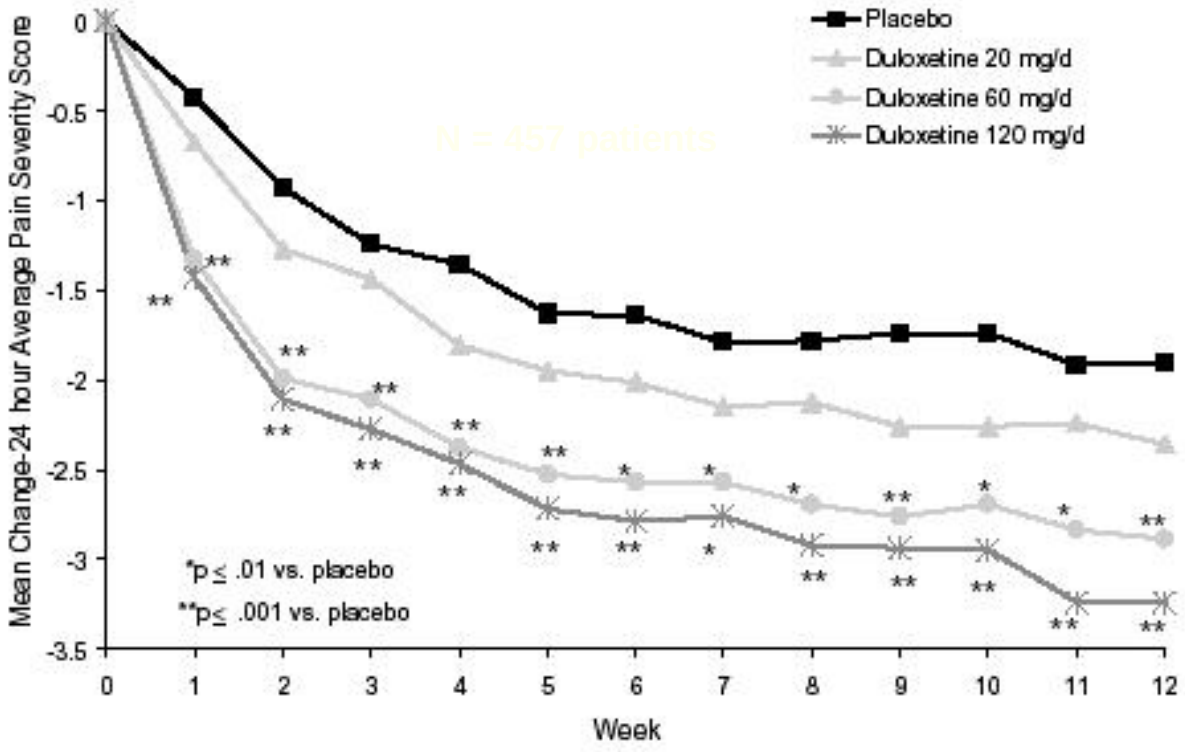
DRG = Dorsal root ganglion;
NS = Nociceptive-specific cells;
PAG = Periaqueductal grey;
PB = Parabrachial area;
RVM = Rostral ventromedial medulla;
WDR = Wide dynamic range.

D'Mello RD, Dickenson AH. *Br J Anaesth.* 2008;101:8–16.

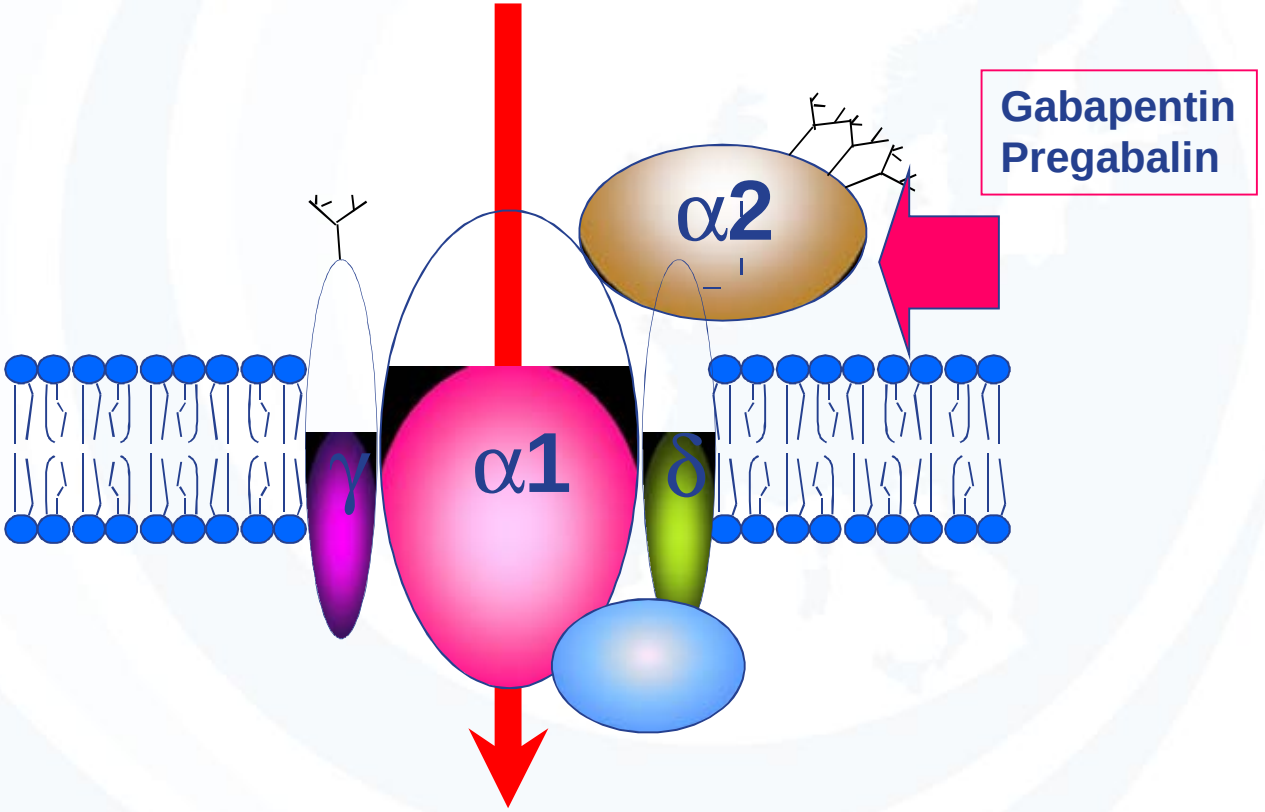
PAIN

Duloxetine vs. placebo in patients with painful diabetic neuropathy*

David J. Goldstein[a], Yili Lu[b], Michael J. Detke[b,c,d,e], Thomas C. Lee[b], Smriti Iyengar[b]

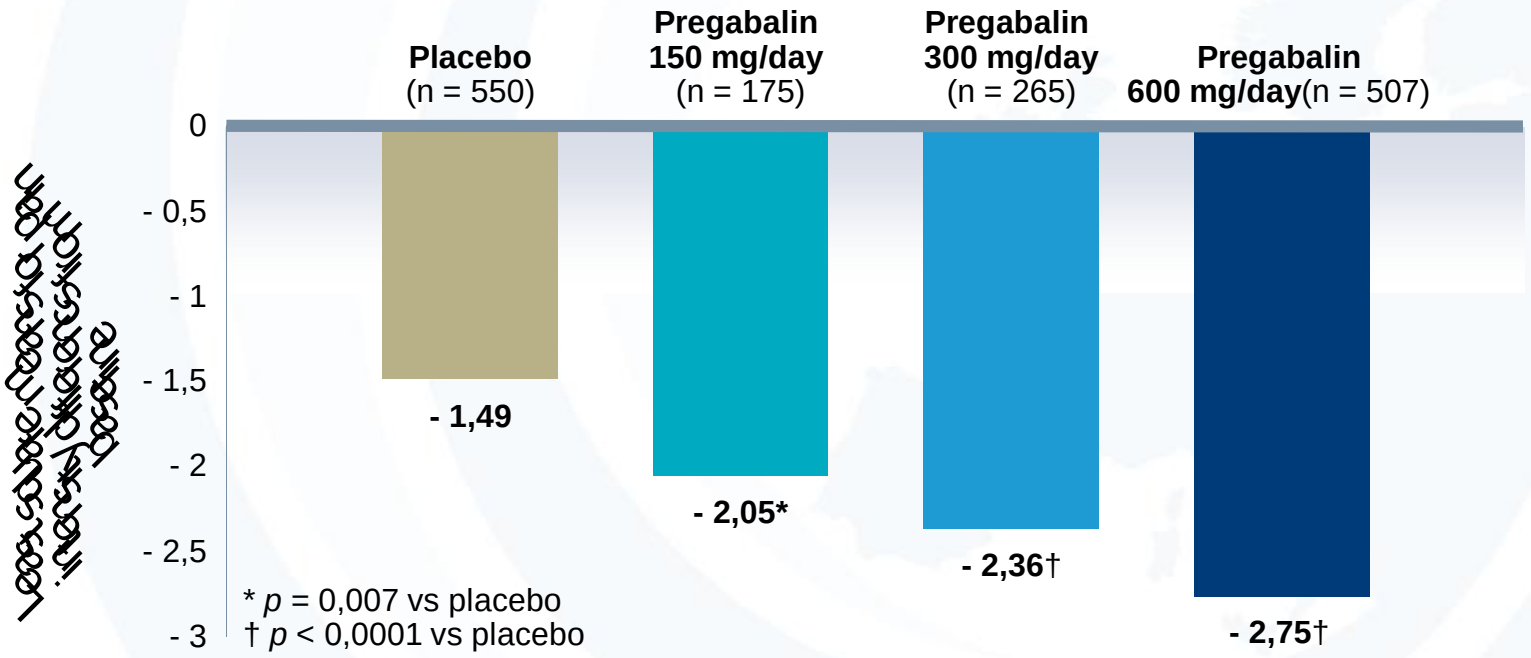


Alpha2delta agonists
Pregabalin and gabapentin



Neurotransmitters release
Neuronal excitability

Pregabalin : a dose-response efficacy



Freeman et al Diabetes Care ; 2008: 31: 1448-1454.

Gabapentin enarcarbil

- Tranported prodrug of gapapentin
- Provides sustained dose proportional exposure to gabapentin
- Absorbed through the intestinal tract by high capacity nutrient transporters and rapidly hydrolysed to gabapentin
- FDA approved for the treatment of restless leg syndrome

Gabapentin enacarbil and neuropathic pain

- 2 positive placebo controlled RCTs in postherpetic neuralgia [1, 2]
- One negative study in diabetic neuropathy : none of 3 treatment groups (1200, 2400, 3600 mg) differentiated from placebo ; active control 300 mg pregabalin negative [3]
- Doses 1200 mg (624 mg equivalent gabapentin) to 3600 mg administered twice daily

[1] Zhang et al J Pain 2013; 14: 590-603; [2] Backonja et al Pain Med 2011; 12: 1098-108;
[3] Rauck et al Pain Pract 2013; 13: 485-496.

Gabapentin enacarbil : does it add anything new ?

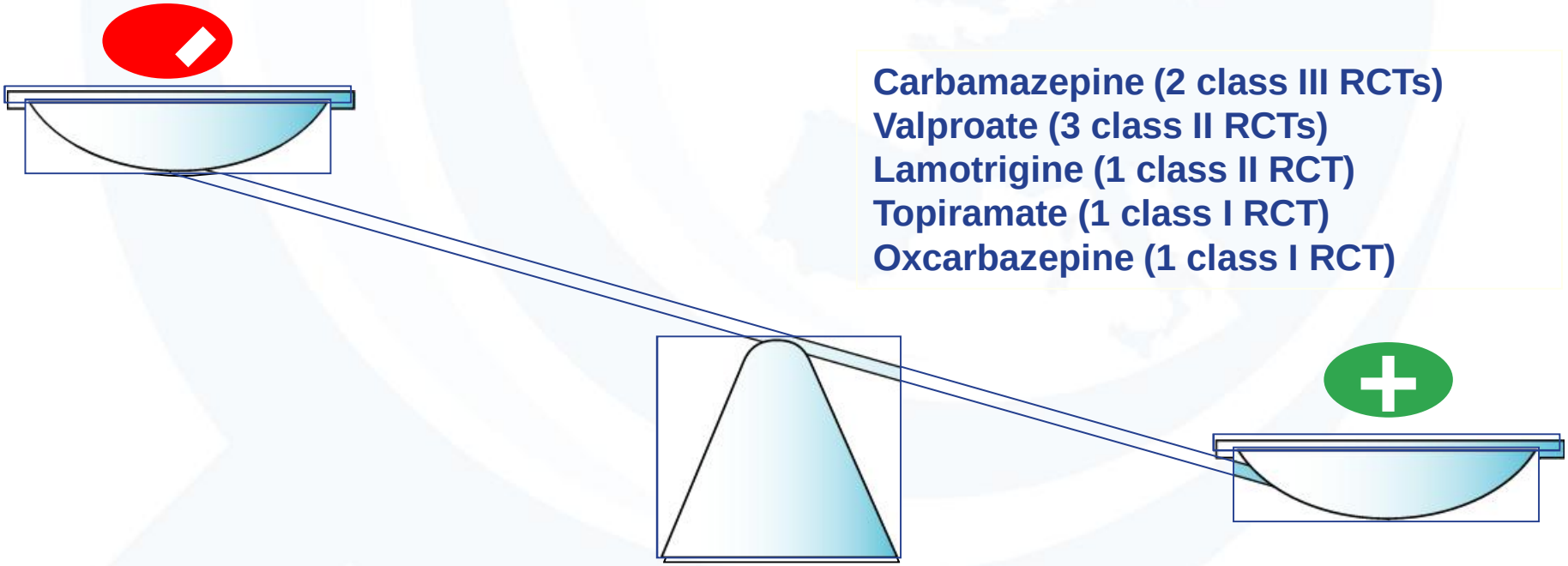
- Better dose response for gabapentin enacarbil than for gabapentin and significant increase in steady state gabapentin concentrations vs gabapentin ; however prebagalin also has dose response efficacy

- It is not clear that that results obtained with these newer gabapentin formulations translate into better efficacy or side effect profile as compared to gabapentin or pregabalin

Other antiepileptics

Contrasting results in diabetic neuropathic pain

Valproate (1 class I RCT)
Lamotrigine (2 class I RCTs)
Topiramate (3 class I studies)
Oxcarbazepine (2 class I RCTs)
Levetiracetam (1 class I RCT)
Zonisamide (1 class I RCT)



Carbamazepine (2 class III RCTs)
Valproate (3 class II RCTs)
Lamotrigine (1 class II RCT)
Topiramate (1 class I RCT)
Oxcarbazepine (1 class I RCT)

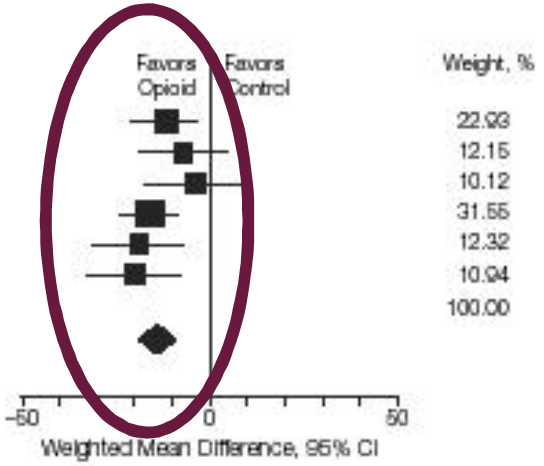
Opioids and neuropathic pain

Figure 4. Results of the Meta-analysis of Intermediate-term Trial Efficacy

Source	Opioid No.	Opioid Posttreatment Pain Intensity, Mean (SD)	Placebo No.	Placebo Posttreatment Pain Intensity, Mean (SD)	Weighted Mean Difference (95% CI)	Weight, %
Gimbel et al,[21] 2003	82	41.00 (27.00)	77	53.00 (26.00)	−12.00 (−20.24 to −3.76)	22.93
Huse et al,[28] 2001	12	33.00 (16.00)	12	40.00 (12.00)	−7.00 (−18.32 to 4.32)	12.15
Morley et al,[22] 2003	19	60.00 (20.00)	19	64.00 (19.00)	−4.00 (−16.40 to 8.40)	10.12
Raja et al,[23] 2002	76	44.00 (24.00)	76	60.00 (20.00)	−16.00 (−23.02 to −8.98)	31.55
Watson and Babul,[27] 1998	39	35.00 (25.00)	39	54.00 (25.00)	−19.00 (−30.24 to −7.76)	12.32
Watson and Babul,[32] 2003	36	26.30 (24.70)	36	46.70 (26.90)	−20.40 (−32.33 to −8.47)	10.94
Total (95% CI)	263		258		−13.63 (−17.57 to −9.68)	100.00

Test for Heterogeneity: $\chi^2_6 = 6.34$ ($P = .27$), $I^2 = 21.1\%$

Test for Overall Effect: $Z = 6.77$ ($P < .001$)



Eisenberg et al JAMA 2005

Tramadol and painful neuropathies

**P*≤0.001 vs placebo

Sindrup et al. Pain. 1999;83:85-90

Tapentadol versus tramadol

Tramadol

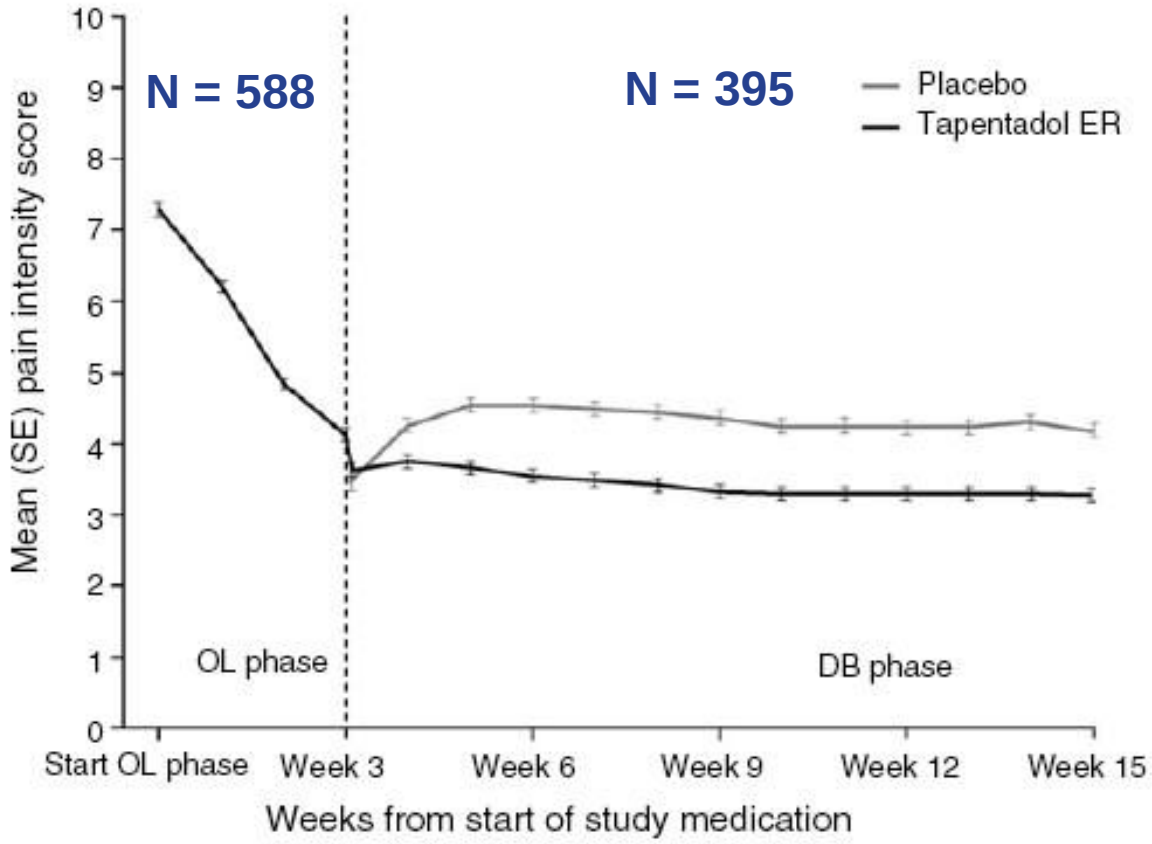
- Weak μ opioid agonist
- Balanced NE/5HT reuptake inhibition

Tapentadol

- Strong μ opioid agonist
- Predominant NE reuptake inhibition

Raffa et al Expert Opin Pharmacother 2012; 13: 1437-49.

Tapentadol and painful diabetic neuropathy



Schwartz et al Curr Med Res Op 2011

Tapentadol versus strong opioids/tramadol in neuropathic pain

- No direct comparative data
- Few GI side effects/oxycodone in other chronic pain conditions

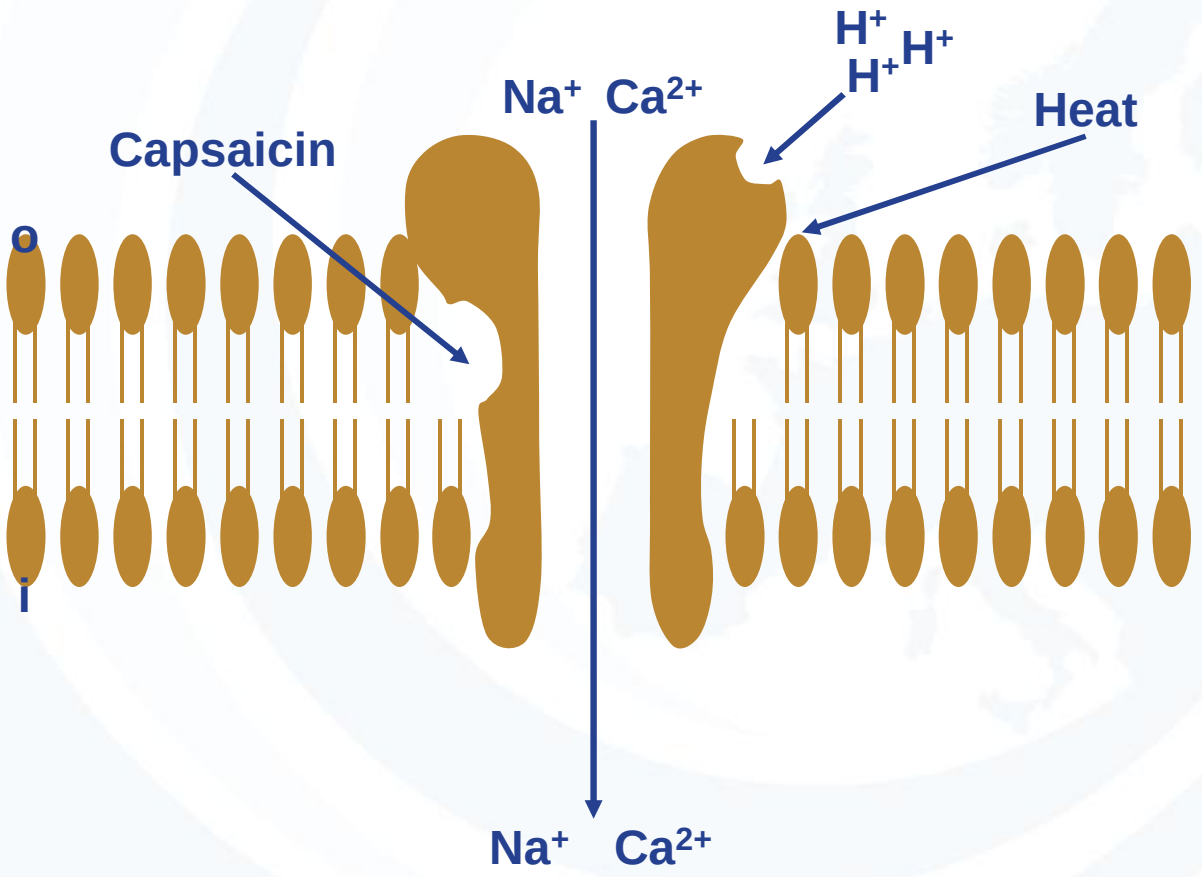
Topical anaesthetics

Lidocaine patches 5%

EMEA and FDA approval (postherpetic neuralgia)

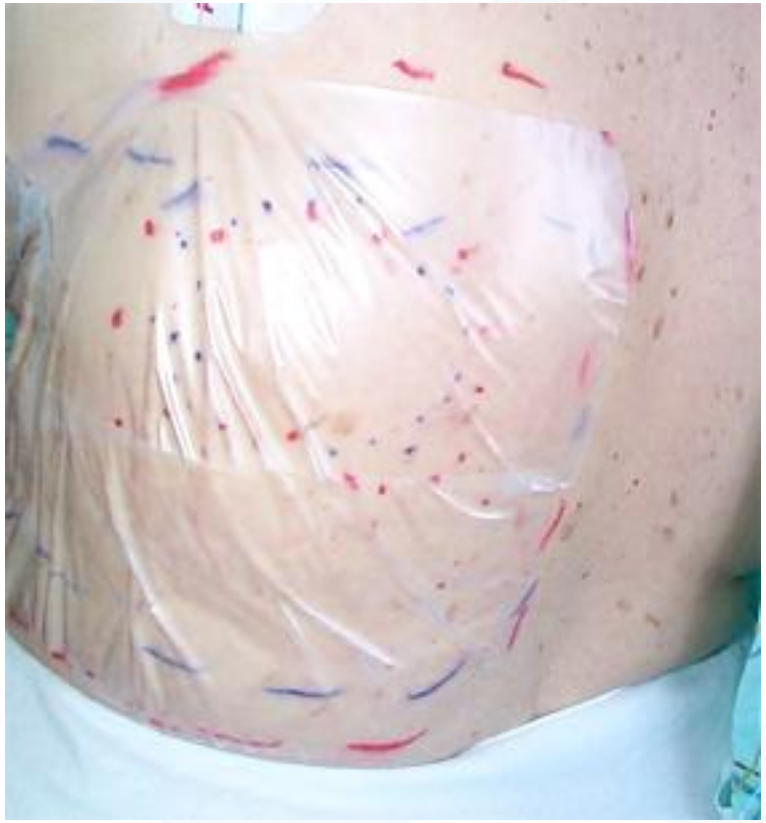
Galer et al Pain 2002; Meier et al Pain 2003 ; Baron et al 2009

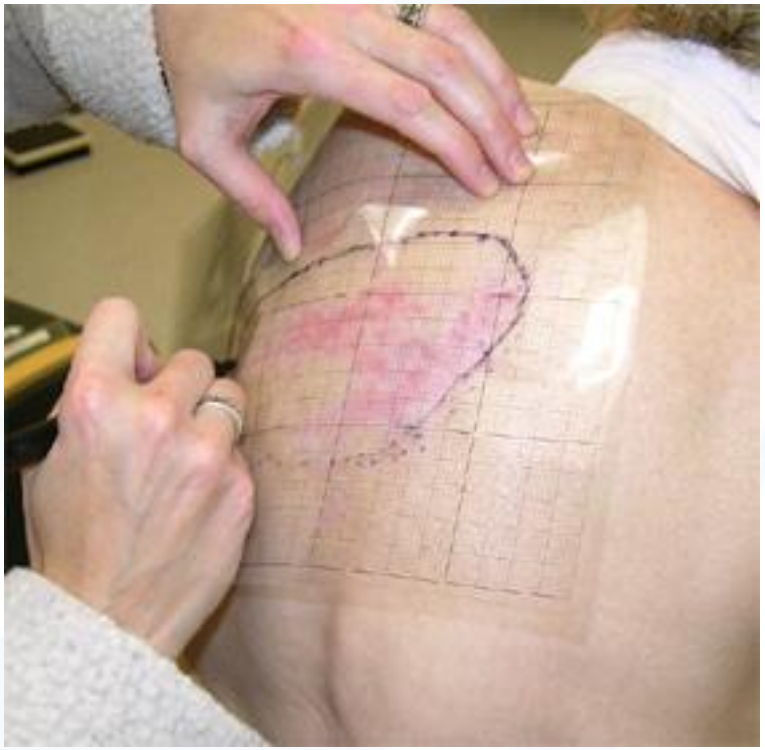
Capsaicin: a TRPV1 agonist



Tominaga and Julius 2001

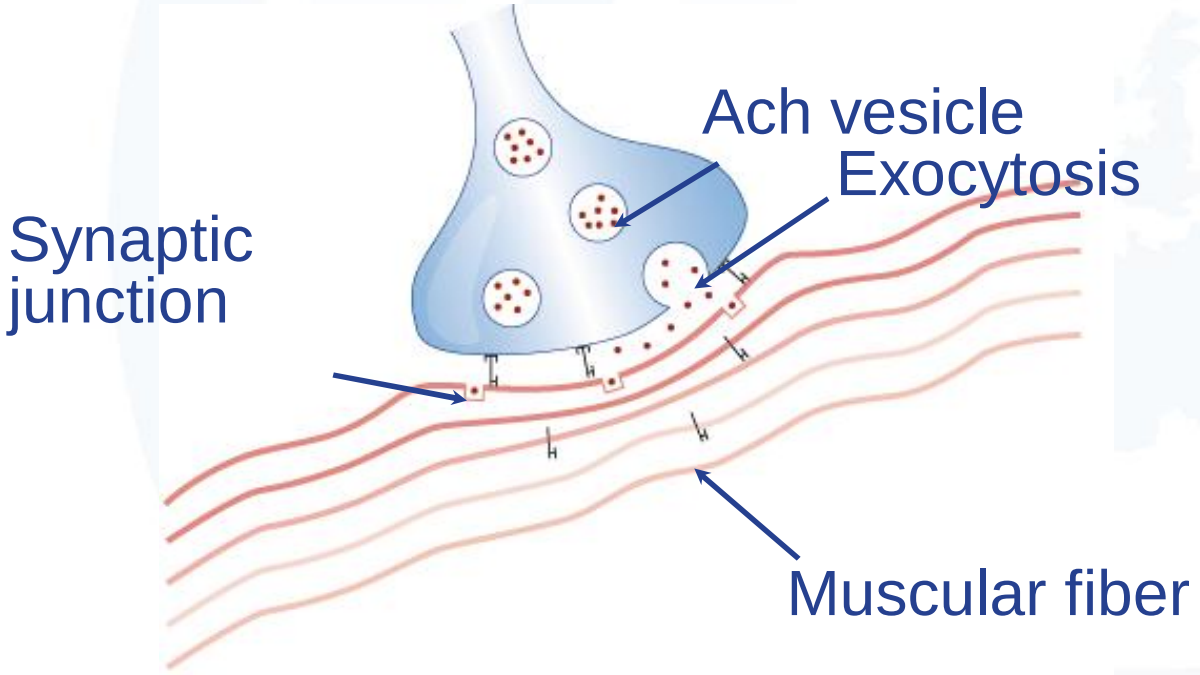
Capsaicin patches (8%) : only approved for non diabetic neuropathic pain





Slide : M. Backonja (2008)

Botulinum toxin inhibits Ach release at the neuromuscular junction



Slide: D. Ranoux

Botulinum toxin (BTX) and non muscular pain

- Analgesic effects in dystonia *(Tsui 1986, Brin 1987)*
  - Early analgesic effect before the antidystonic effect
  - More important than would be expected from the effect on hypertonia

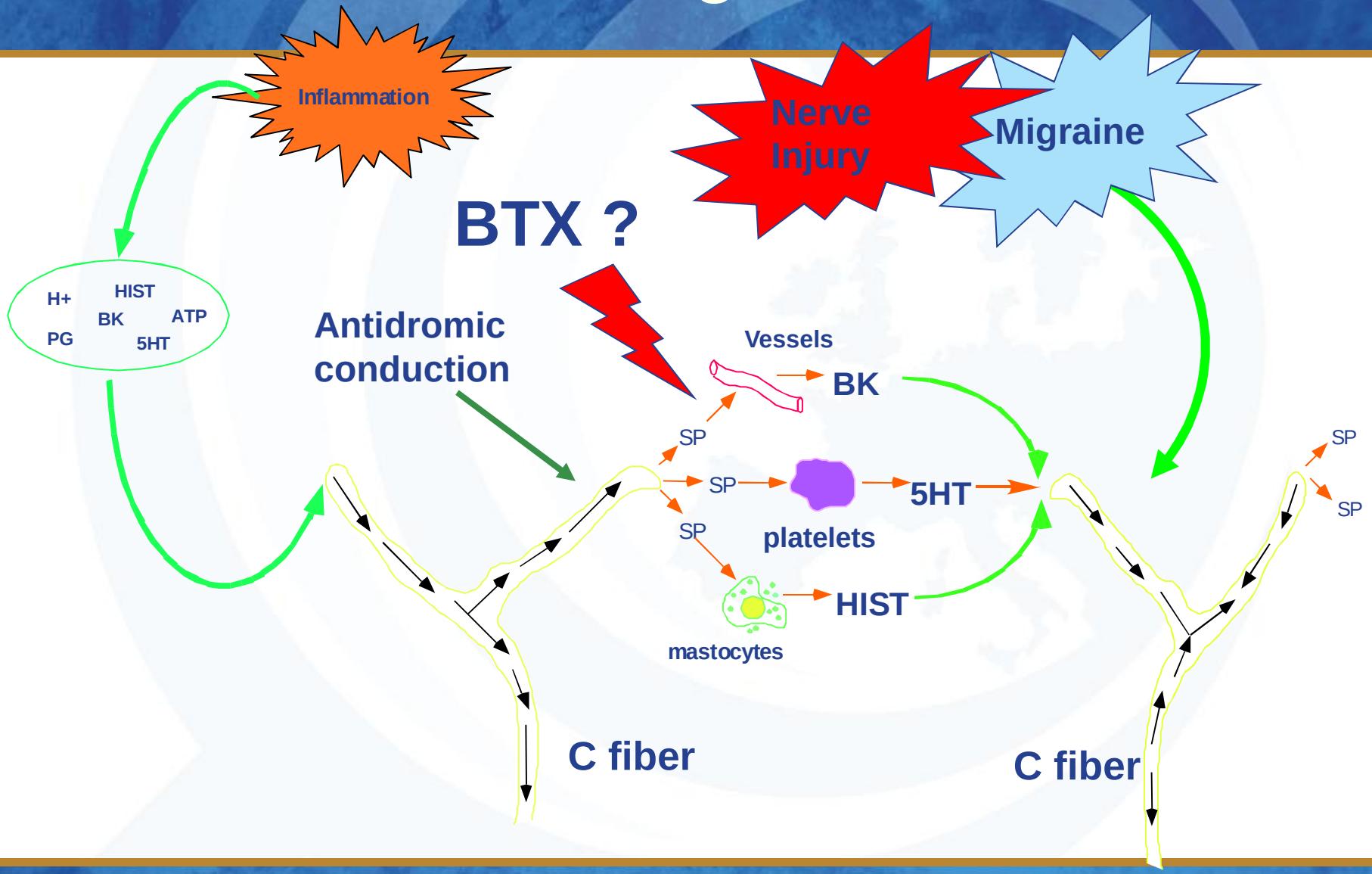
- Effects on chronic migraine (Preempt studies)

  (e.g. Silverstein et al 2013)

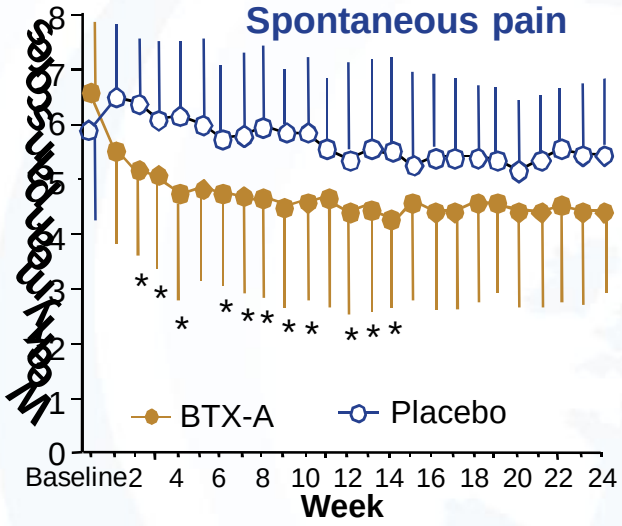
- Sustained antiallodynic effects on animal models of neuropathy

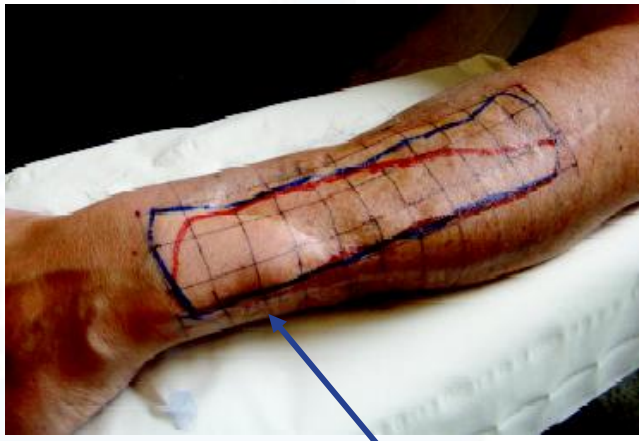
  (e.g. Bach-Rojecky et al E J Pharmacol 2010; Luvisetto et al Neuroscience 2007; Favre-Guimard et al E J Pharmacol 2009)

Effects on neurogenic inflammation

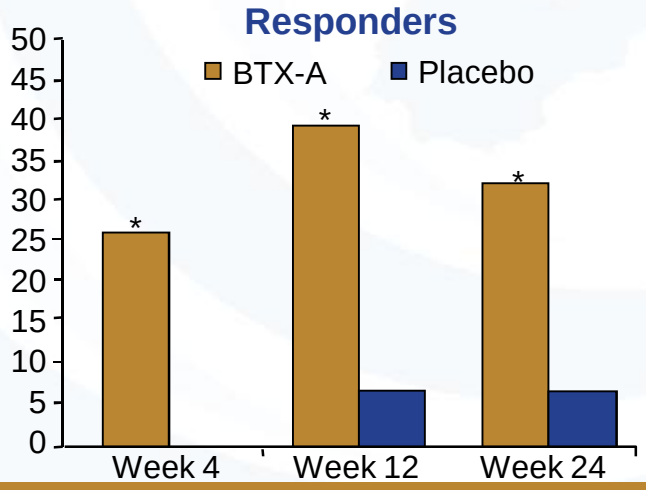


Botulinum toxin A (BTX-A) in focal painful neuropathy with allodynia



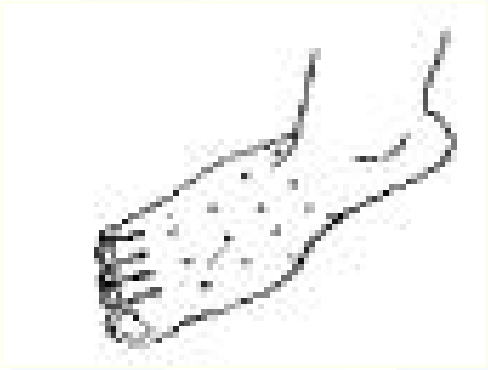


SC injection

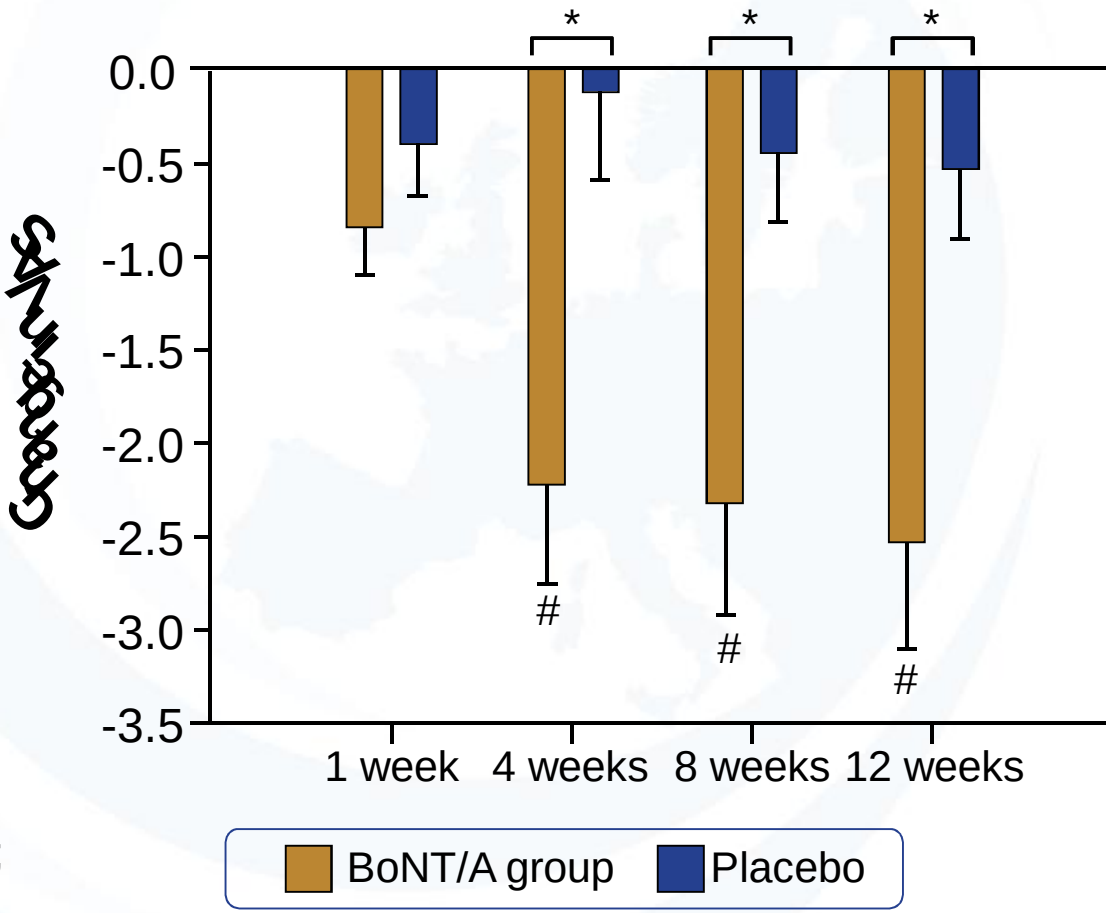


Ranoux et al. Ann Neurol 2008;64:274-83

Botulinum toxin for diabetic neuropathic pain – a randomized double-blind crossover trial



50 U BoNT/A 1.2 mL with
12 intradermal injections



#p<0.05 by comparison with 0 ;
*p<0.05 between groups.

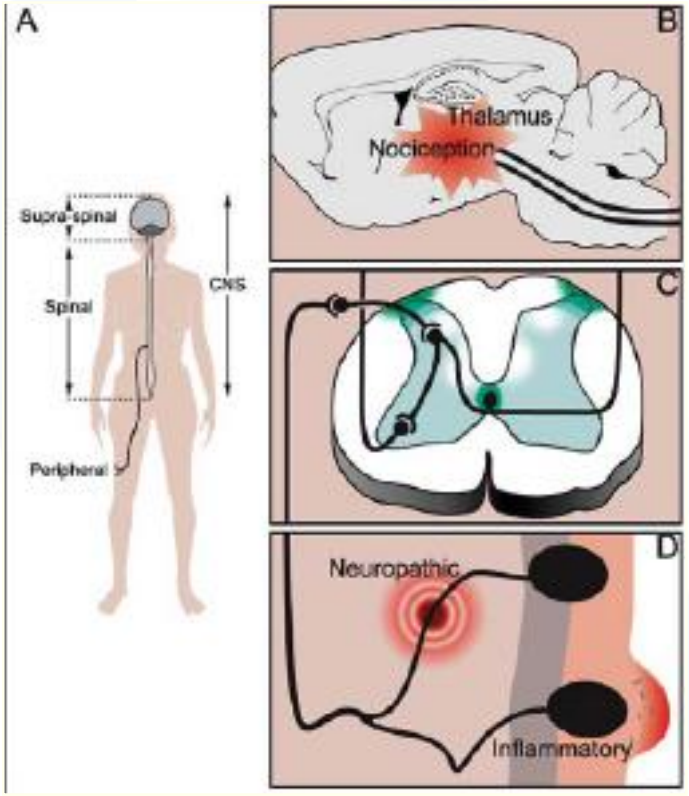
Yuan et al. Neurology 2009

Side effects

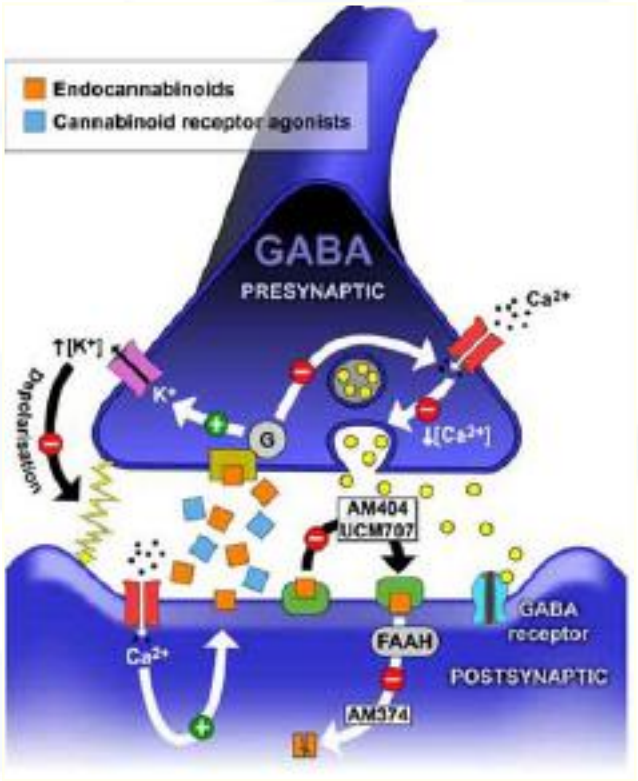
- No systemic or motor side effects
- Pain related to the injection particularly in the hands (++ necessity of analgesic procedures and experienced clinician)

Cannabinoids and pain control

CB1 and CB2 receptors

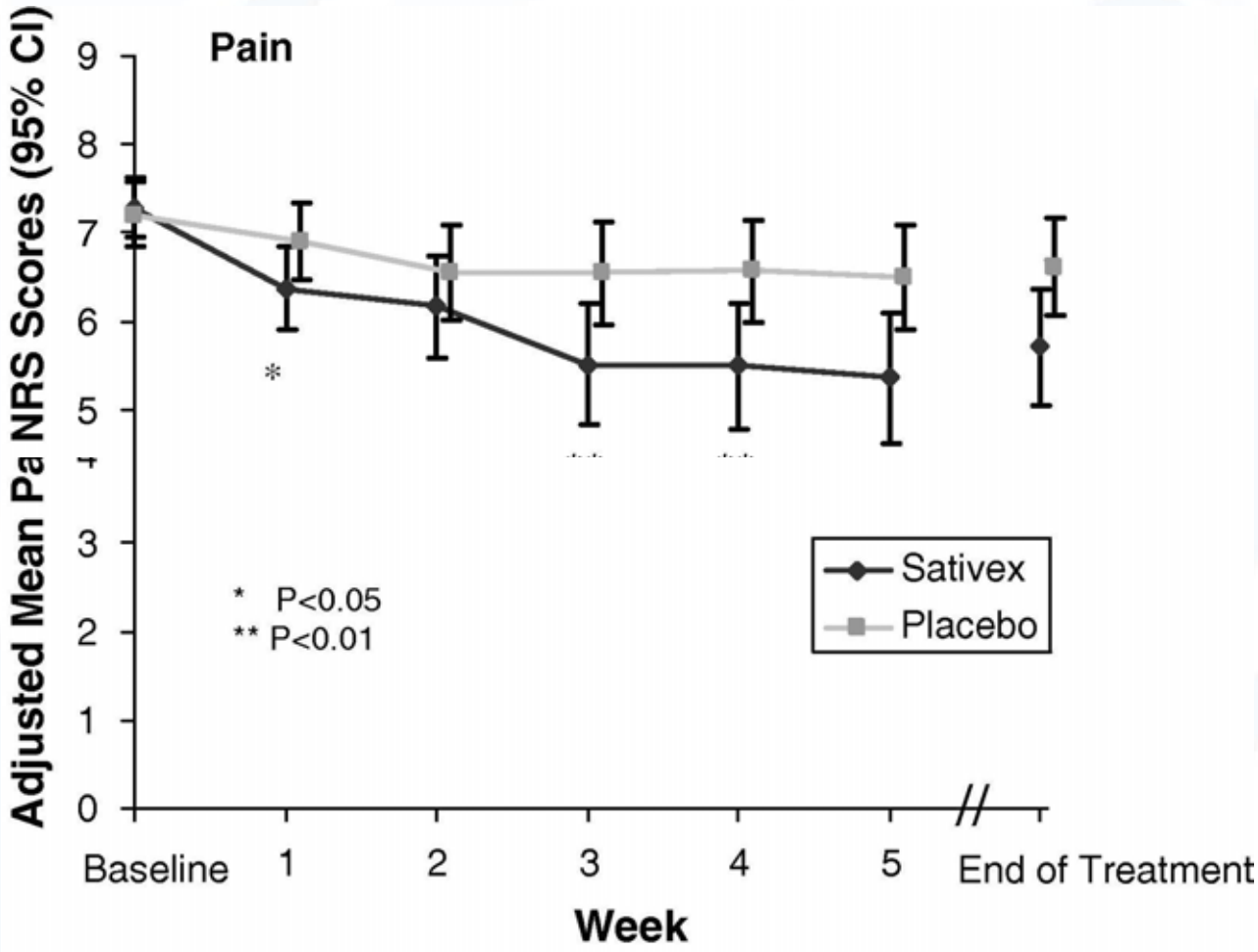


GABAergic synapse (containing CB1 R)



Manzarane et al 2006 ; Maione et al Pain 2013

Sativex and peripheral neuropathic pain



Nurmikko et al Pain 2007

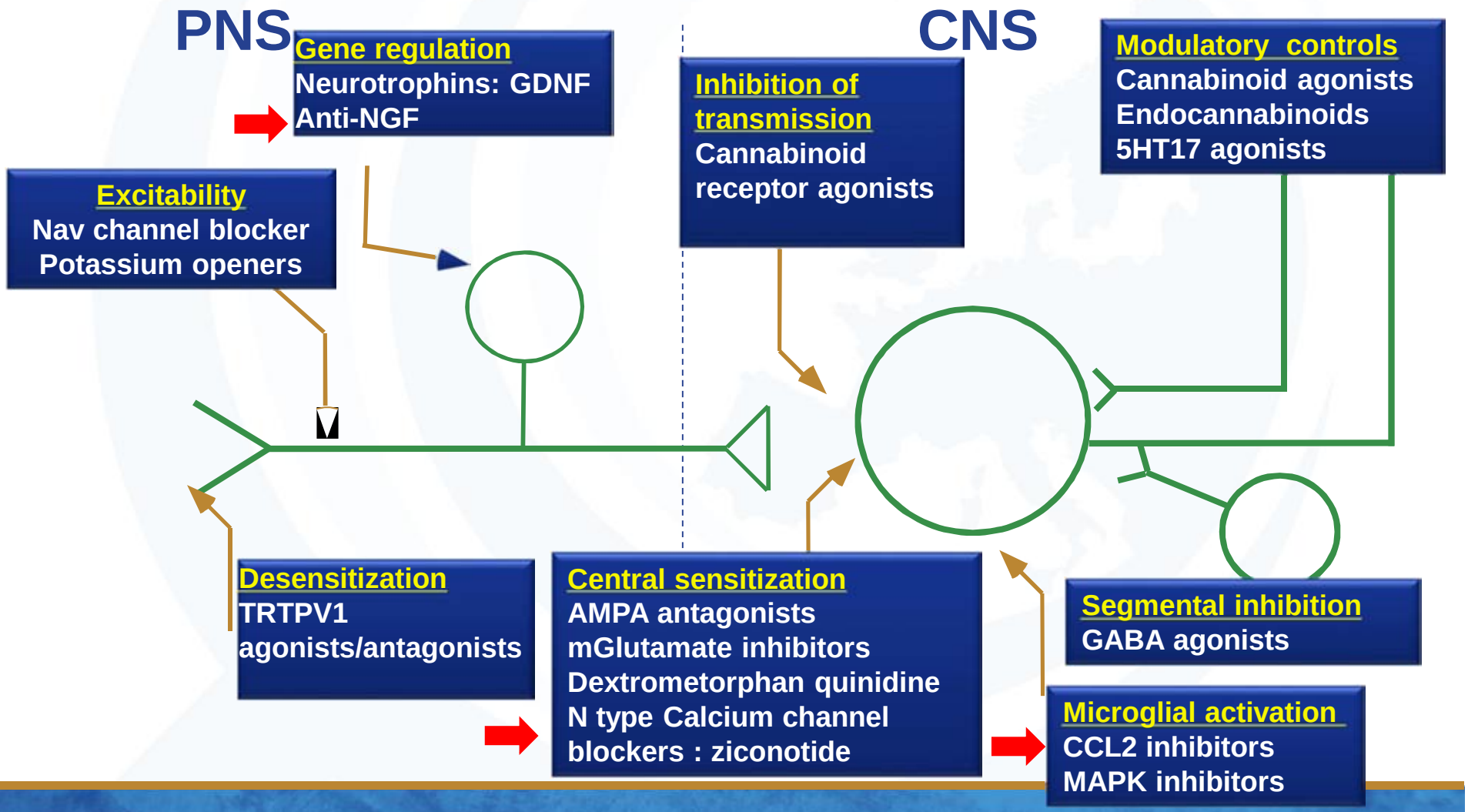
Summary of guideline recommendations for diabetic painful neuropathies

Guide-line	Condition examined	TCAs	SNRIs Duloxetine venlafaxine	α2δ-ligands pregabalin gabapentin	Opioids
EFNS	NP	1st line	1st line (duloxetine)	1st line	2nd line
NeuPsig (IASP)	NP	1st line	1st line	1st line	2nd line
NICE (UK)	NP	1st line (ami) if duloxetine CI	1st line	2nd line	2nd line (tramadol)
AAN (USA)	Diabetic NP	2nd line	2nd line	1st line (pregabalin)	2nd line

NP : neuropathic pain ; TCAs : tricyclic antidepressants ; ami : amitriptyline ; CI : contraindicated

Adapted from Spallone Curr Diab Rep 2012

New targets for neuropathic pain



How to improve therapeutic outcome ?

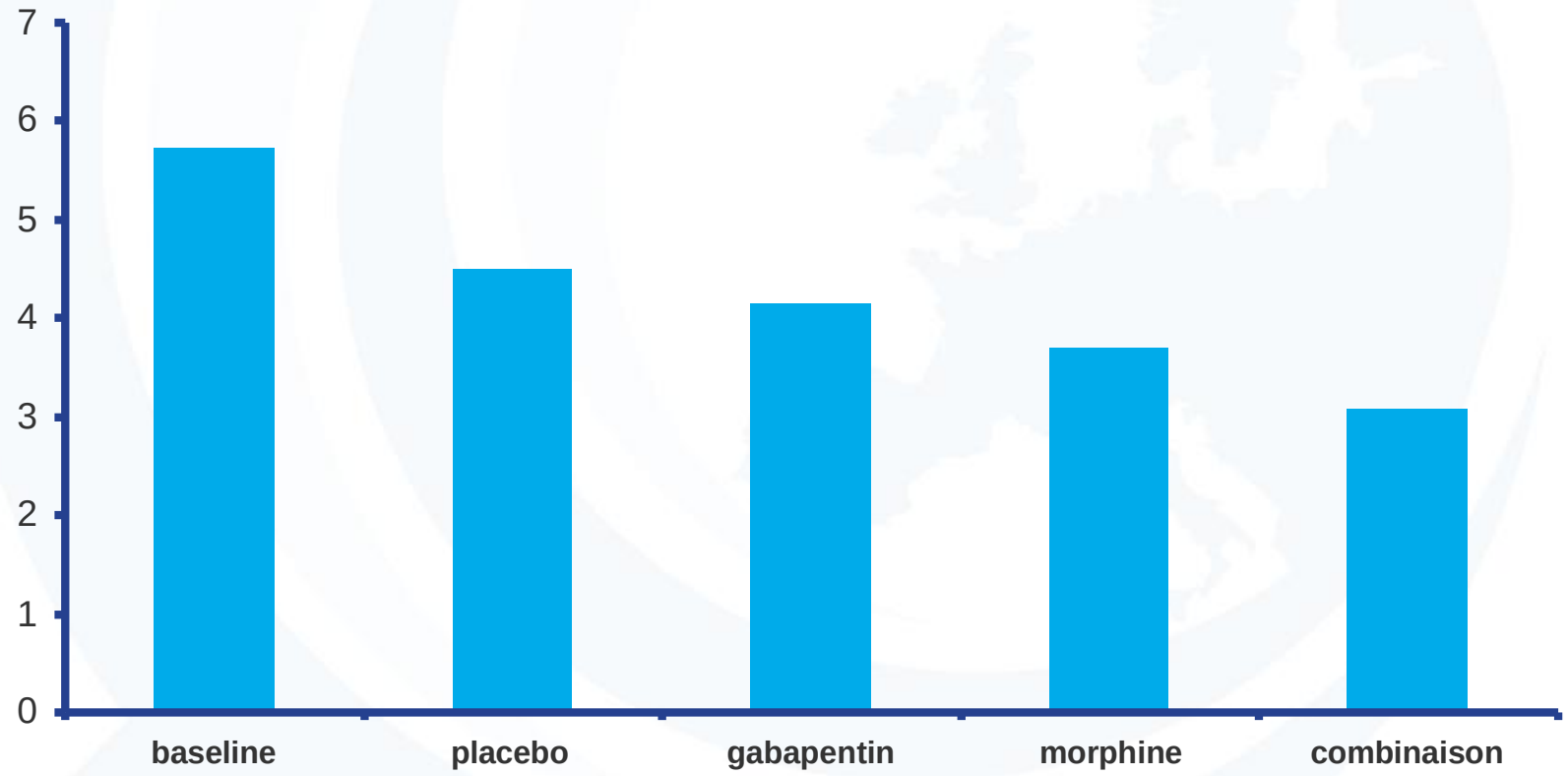
- Use combination therapy

- Use new study designs

- Enrichment designs (Hewitt et al Pain 2011)

- Better define responder profiles

Combination therapy



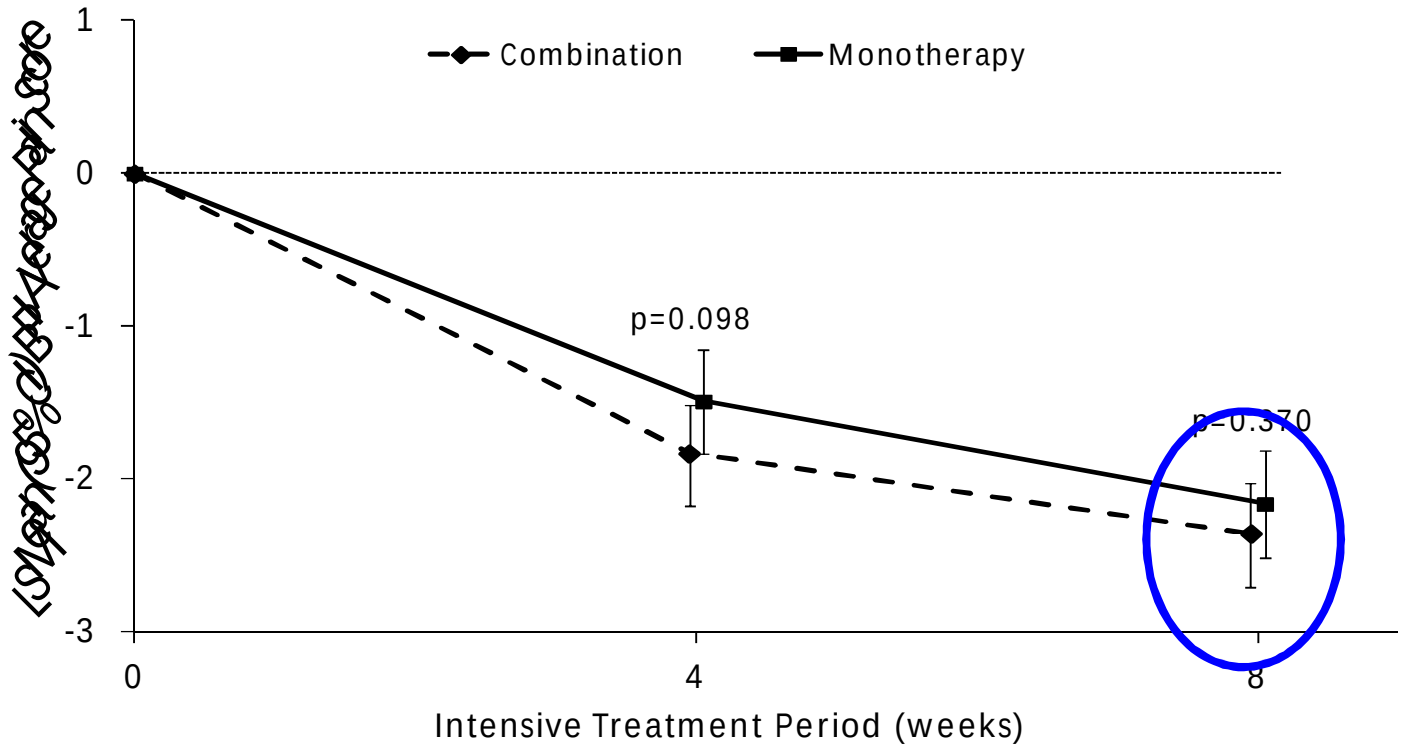
Gilron et al NEJM 2005

The COMBO-DN study
Clinical question

In patients with painful diabetic neuropathy not responsive to first line monotherapy (with pregabalin or duloxetine) : is is more relevant to increase the initial dosage or to associated with another first line drug ?

The COMBO-DN trial

Variation of BPI-MSF – "Average pain over 24 h" – Intensive treatment



BPI-MSF = Brief Pain Inventory Modified Short Form; CI = Intervalle de confiance; LS mean = least squares mean (moyenne des moindres carrés).

Tesfaye et al Pain 2013

How to improve therapeutic outcome ?

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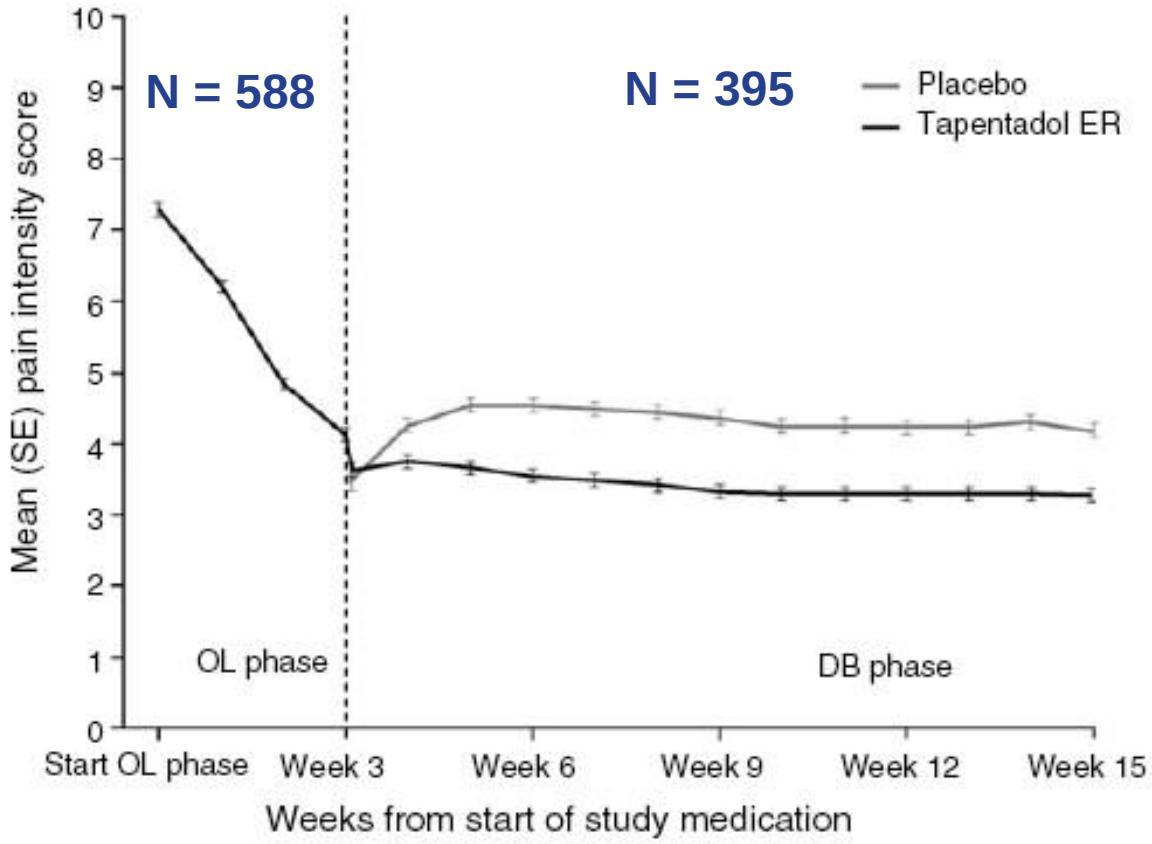
Tapentadol and painful diabetic neuropathy



Schwartz et al Curr Med Res Op 2011

How to improve therapeutic outcome ?

- Use combination therapy
- Use new study designs

- Enrichment designs
- Better define responder profiles (Attal et al E J Pain 2011)

PAIN® xxx (2009) xxx–xxx

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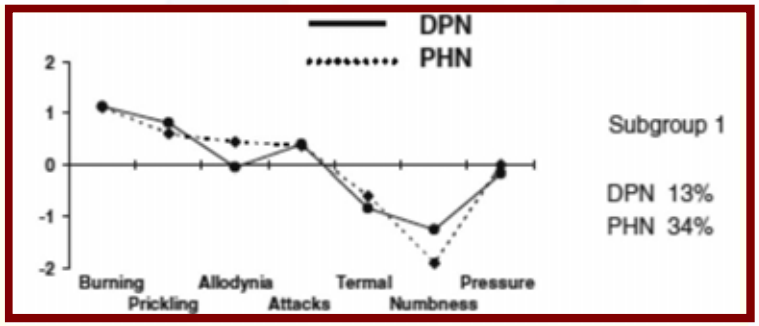
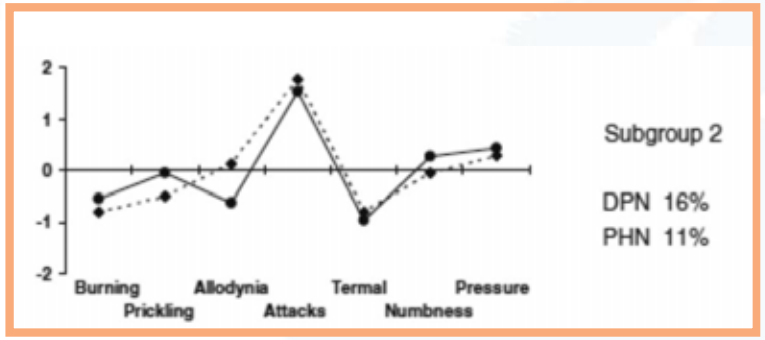
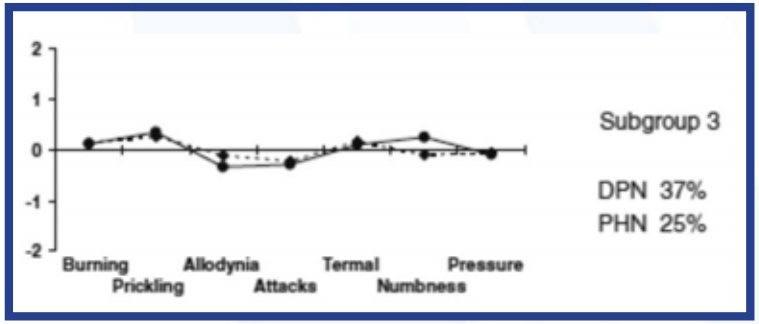
www.elsevier.com/locate/pain

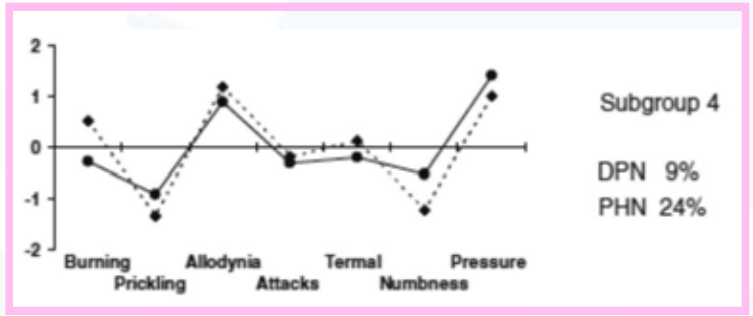
A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: Differences in demographic data and sensory symptoms

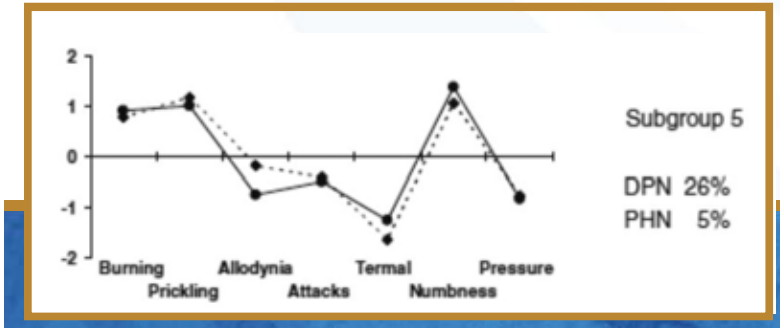
Ralf Baron [a,*], Thomas R. Tölle [b], Ulrich Gockel [c], Mathias Brosz [d], Rainer Freynhagen [e,f]











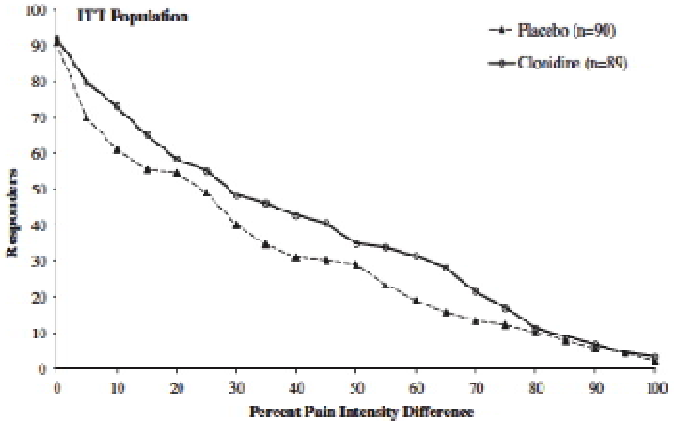
More variability within each aetiology than between aetiologies

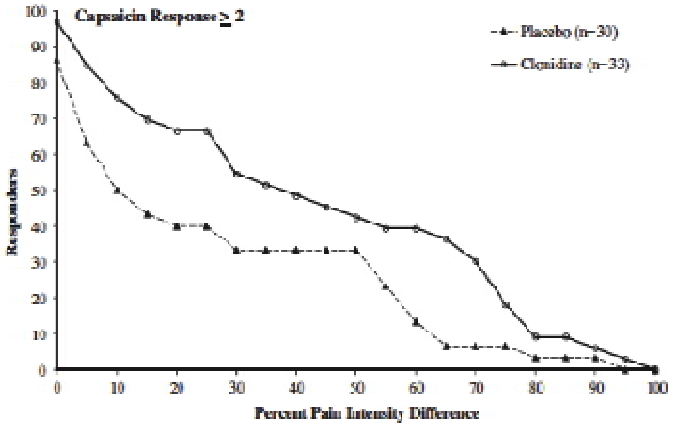
PAIN® 153 (2012) 1815–1823

PAIN®

Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy

Claudia M. Campbell[a,*], Mark S. Kipnes[b], Bruce C. Stouch[c], Kerrie L. Brady[d], Margaret Kelly[d], William R. Schmidt[d], Karin L. Petersen[e,f], Michael C. Rowbotham[e,f], James N. Campbell[d]





Pooled results from 4 negative/weakly positive trials with pregabalin (n= 538 placebo ; n = 693 pregabalin)

Poststroke pain

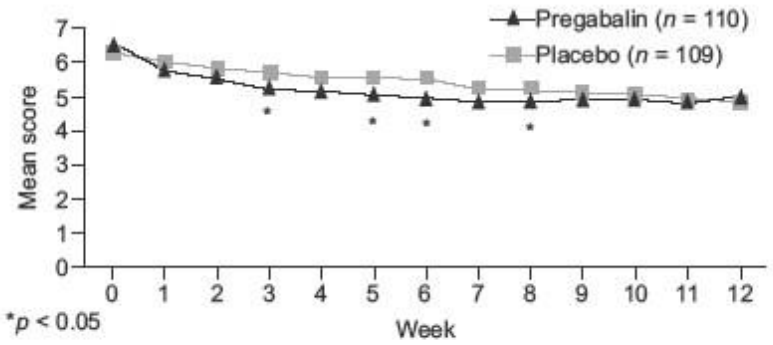
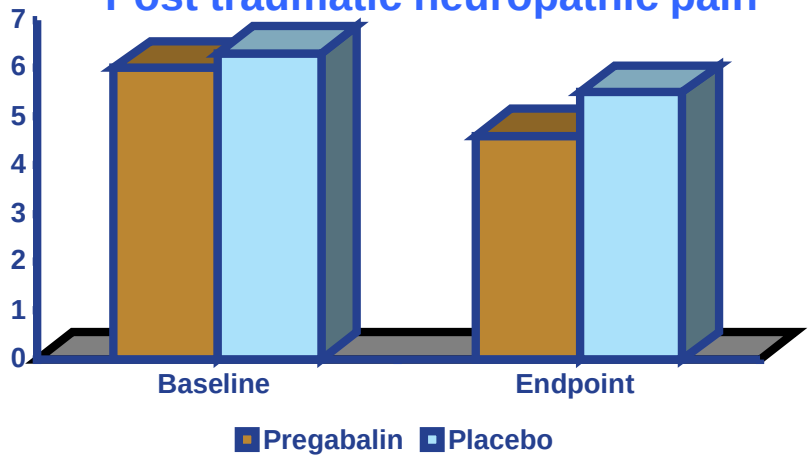


Fig. 2. Weekly mean pain score.

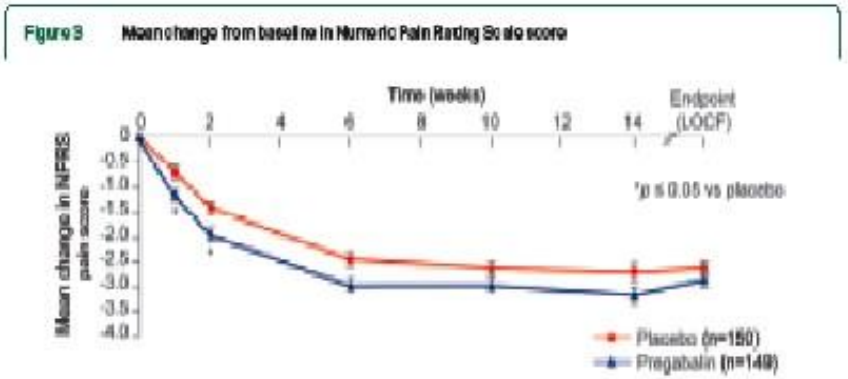
Kim et al Pain 2010

Post traumatic neuropathic pain



Van Seventer et al E J Neurol 2010

HIV neuropathy



Simpson et al Neurology 2010

Diabetic painful neuropathy

Protocol NoA0081071 clinicalstudyresults.org

5 clusters of patients based on a specific questionnaire (NPSI)

3 dimensions : Dimension 1 : burning/paresthesia/electric shocks ; Dimension 2 : deep pain ; Dimension 3 : evoked pain

Cluster 1 Dimension 3	Cluster 2 Dimension 1	Cluster 3 Dimension 1 Dimension 2/3 weak	Cluster 4 Dimension 3 Dimension 2 weak	Cluster 5 Dimension 2
Post stroke 8 % Trauma 23 % HIV 11 % Diabetes 11 %	Post stroke 13 % Trauma 21 % HIV 29 % Diabetes 28 %	Post stroke 7 % Trauma 7 % HIV 15 % Diabetes 28 %	Post stroke 41 % Trauma 19 % HIV 26 % Diabetes 21 %	Post stroke 31 % Trauma 30 % HIV 19 % Diabetes 12 %
No difference/ placebo	Pregabalin > Placebo	Pregabalin > Placebo	No difference /placebo	No difference /placebo

Freeman, Baron, Bouhassira et al, World Congress, PF 371, 14th World Congress on Pain, aug 2012

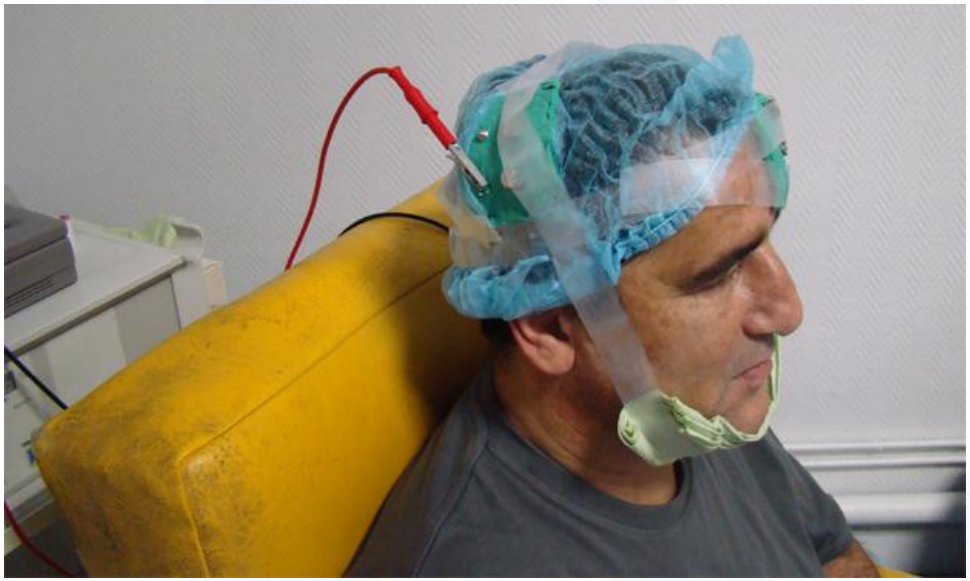
Emerging non drug treatments: Non-invasive cortical stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS)

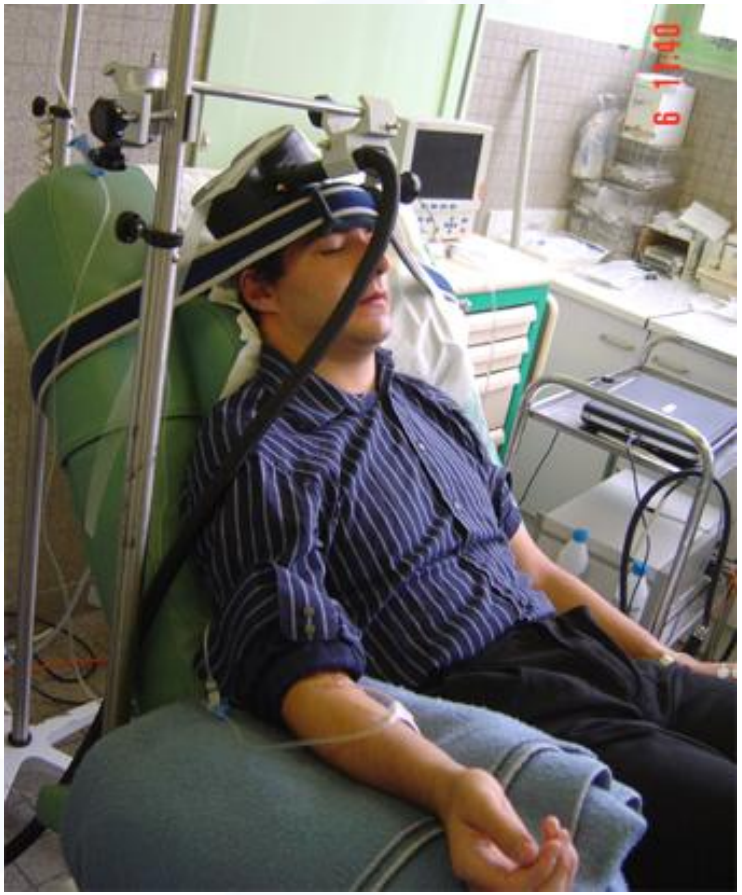
- TMS: neurophysiological tool (Barker et al. Lancet 1985)
- Development of new machines: rTMS (George et al. Neuroreport 1995 and Pascual-Leone et al. Lancet 1996)
- Initial use in psychiatry (depression), tinnitus, stroke rehabilitation, Parkinson disease (Rothwell. Nature Rev Neurosci 2007)
- Use in chronic pain including NP (Lefaucheur et al. Neuroreport 2001; Andre-Obadia et al. Neurology 2008; Khedr et al JNNP 2004; Passard et al. Brain 2007; Mhalla et al Pain 2010)

Transcranial Direct Curent Stimulation (tDCS)

- Mainly used in chronic pain (Fregni et al. Pain 2006a,b; Fregni et al Brain 2010).



right M1 anodal tDCS



right M1 rTMS

Summary

- Drug treatments effective for diabetic NP include tricyclic/SNRI antidepressants, gabapentin, pregabalin, topical lidocaine, opioids and potentially botulinum toxin
- Newer drug treatments include newer opioids (tapentadol), botulinum toxin, and newer gabapentin formulations
- For more refractory patients noninvasive brain stimulation techniques are increasingly proposed