

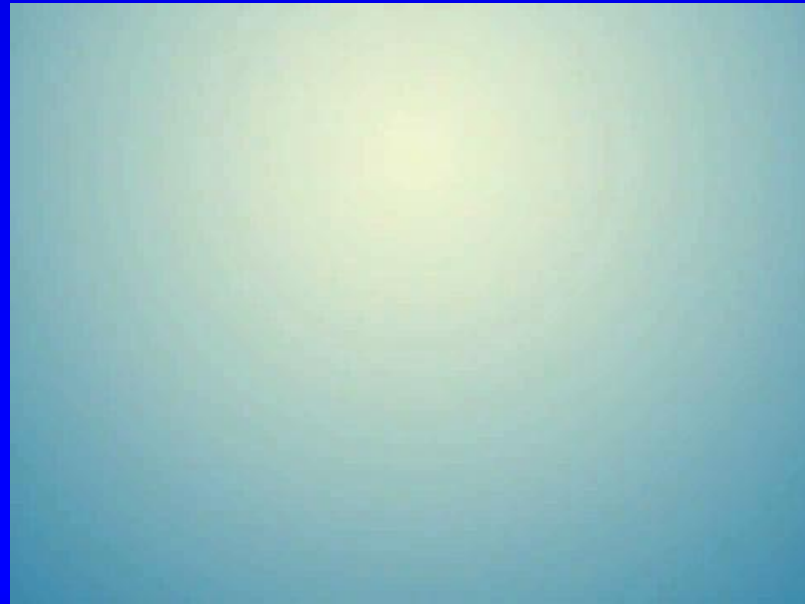
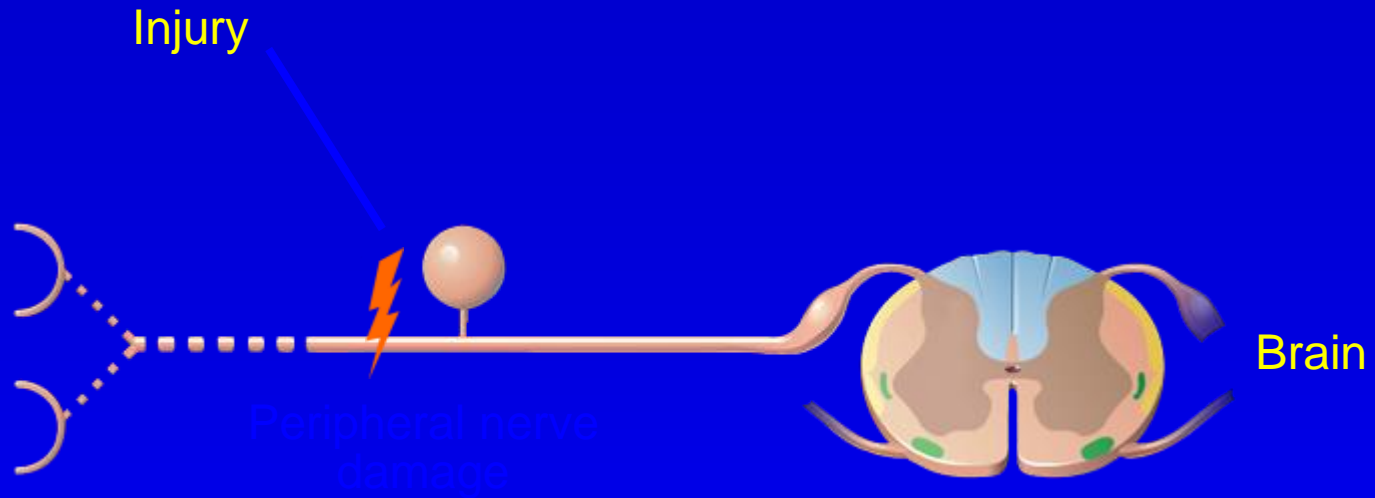
Painful Diabetic Neuropathy

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Children's University Hospitals



Target



Painful Neuropathy



Diagnosis: DN4

- Completed by physician
- Differentiates neuropathic from nociceptive pain
- 2 pain questions (7 items)
- 2 sensitivity tests (3 items)
- Validated
- Sensitivity 82.9%
- Specificity 89.9%

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?

	yes		no
1 - Burning			
2 - Painful cold			
3 - Electric Shocks			

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	yes		no
4 - Tingling			
5 - Pins and Needles			
6 - Numbness			
7 - Itching			

EXAMINATION OF THE PATIENT

Question 3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

	yes		no
8 - Hypoesthesia to touch			
9 - Hypoesthesia to prick			

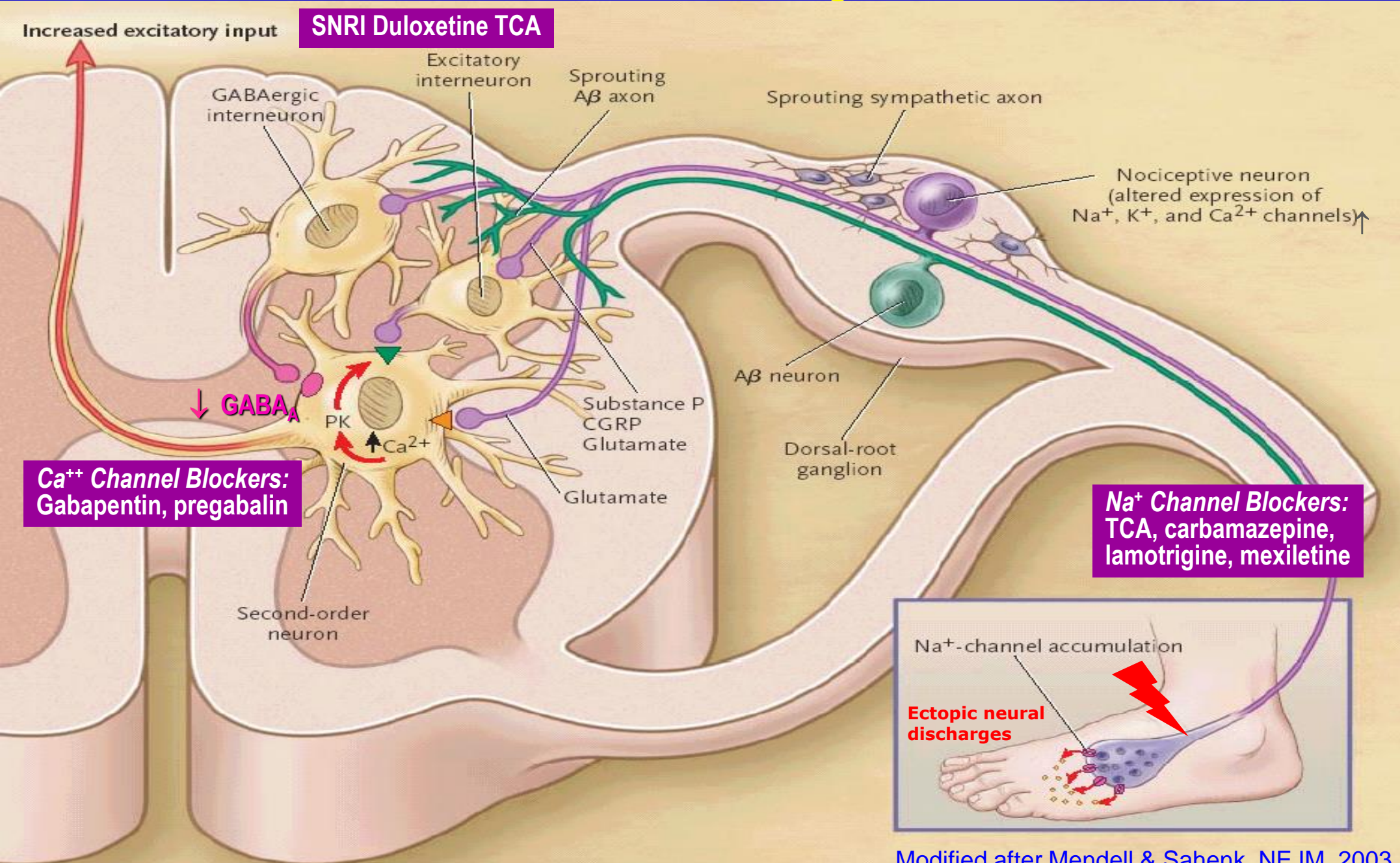
Question 4: In the painful area, can the pain be caused or increased by:

	yes		no
10 - Brushing			

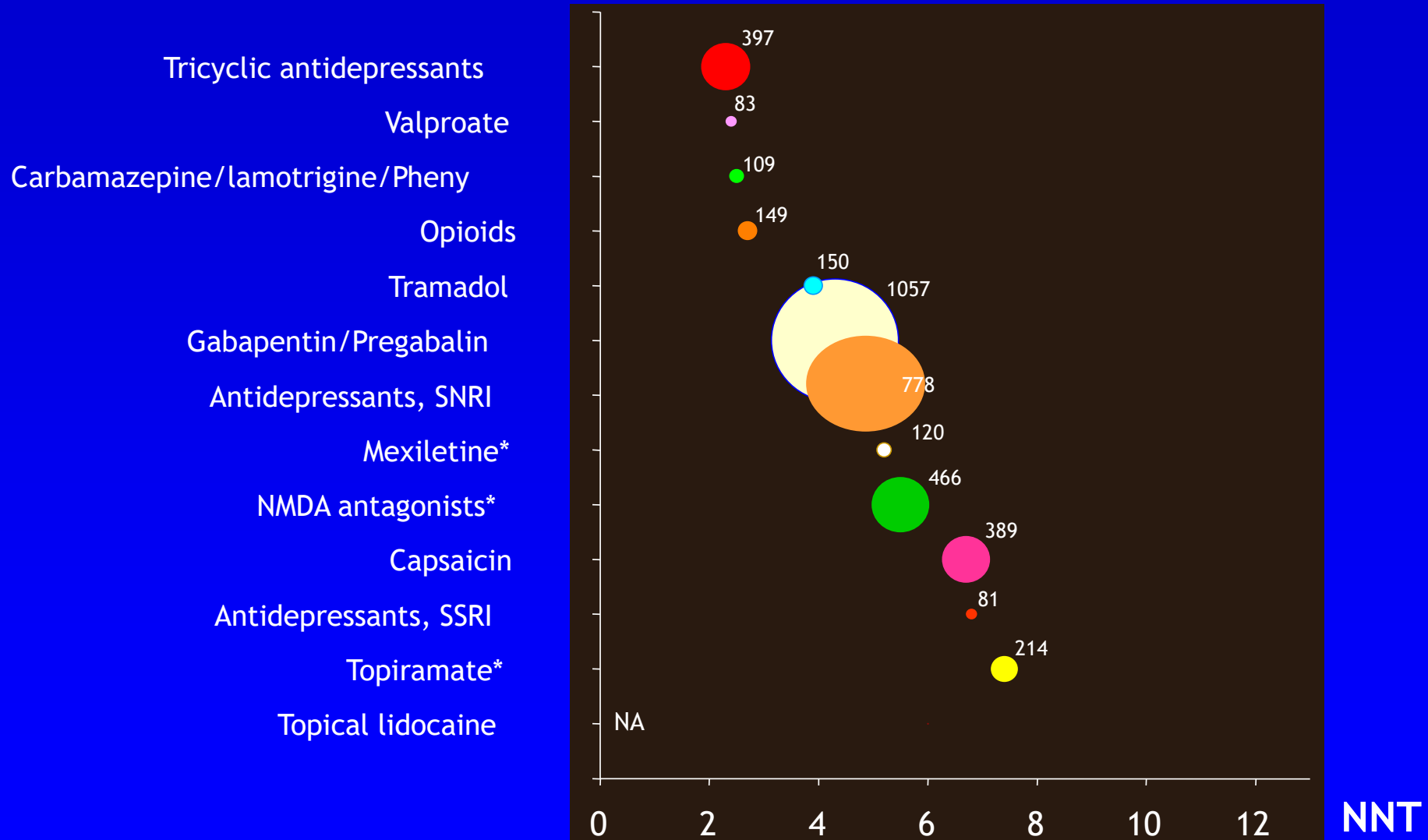
Treatment



Mechanism based Pharmacologic Interventions

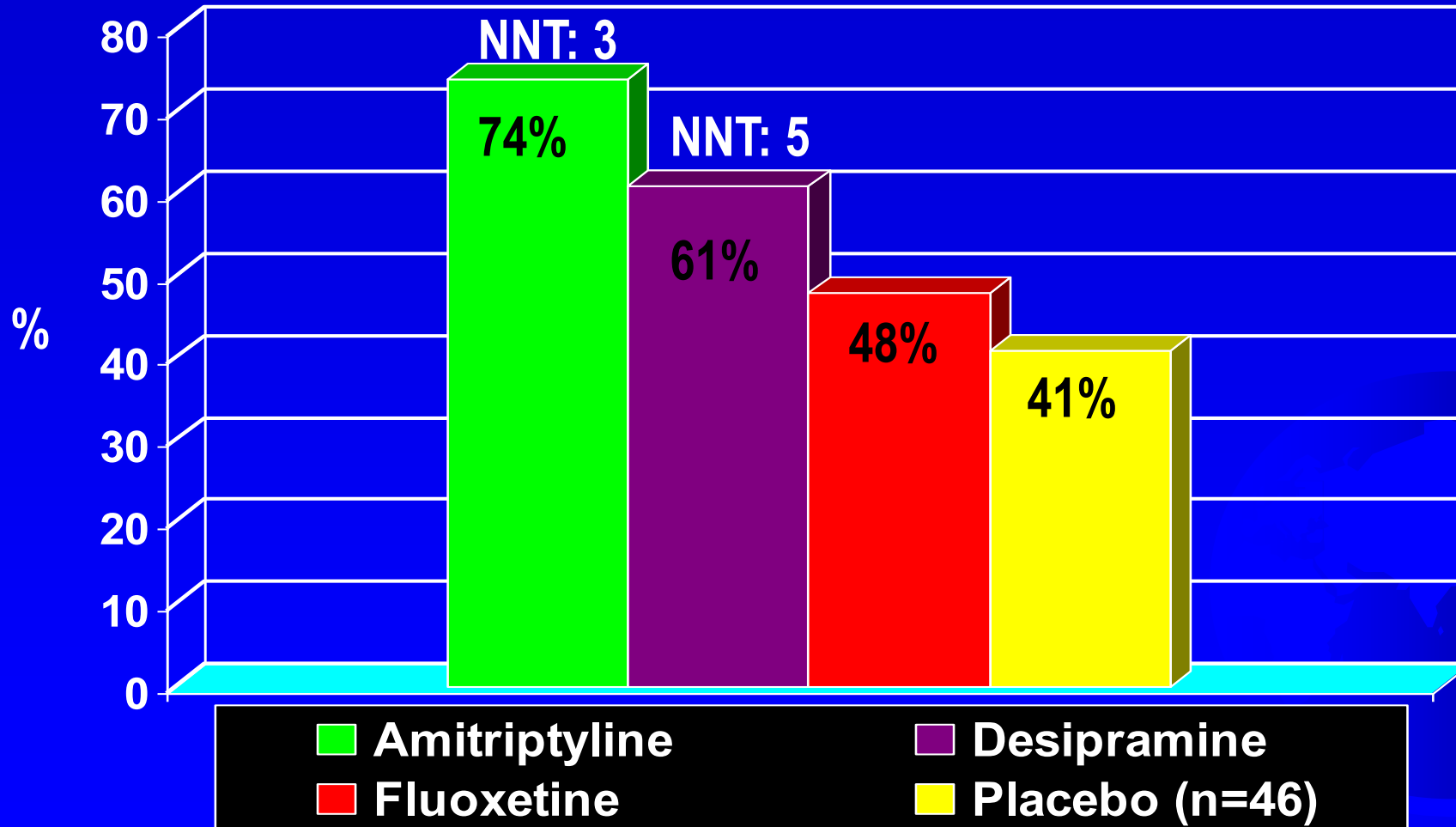


Evidence base



Antidepressants in Painful Diabetic Neuropathy

6-Week Cross-Over Study n=20: $\geq 50\%$ pain relief

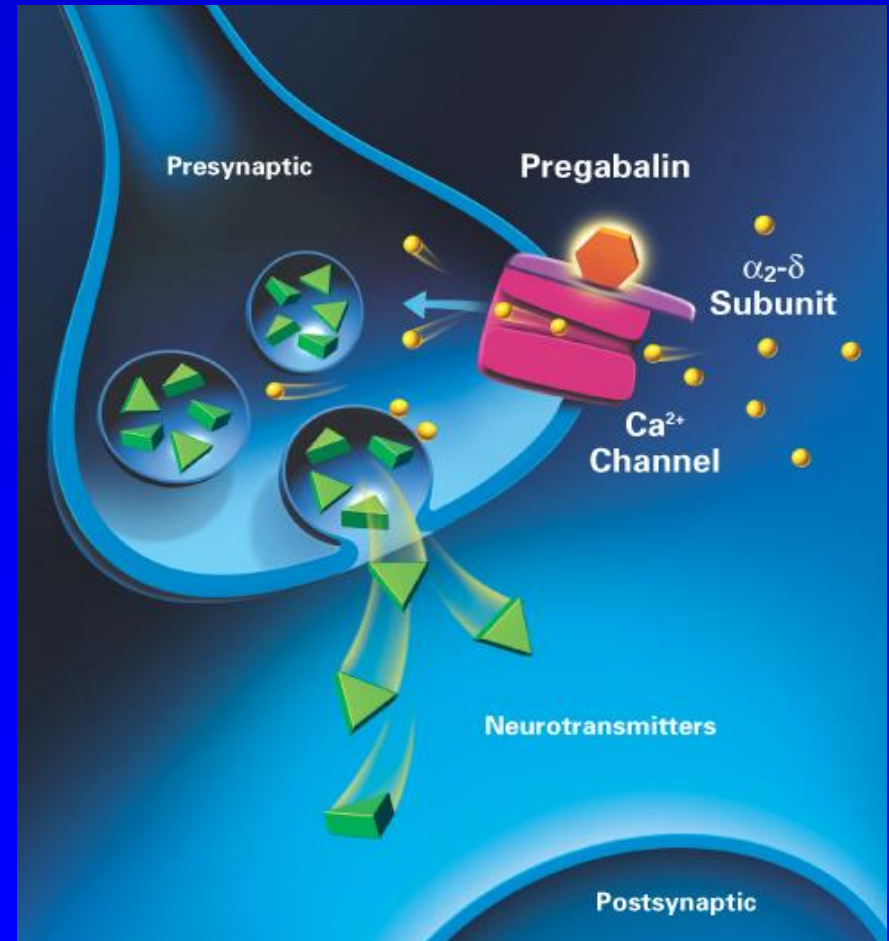
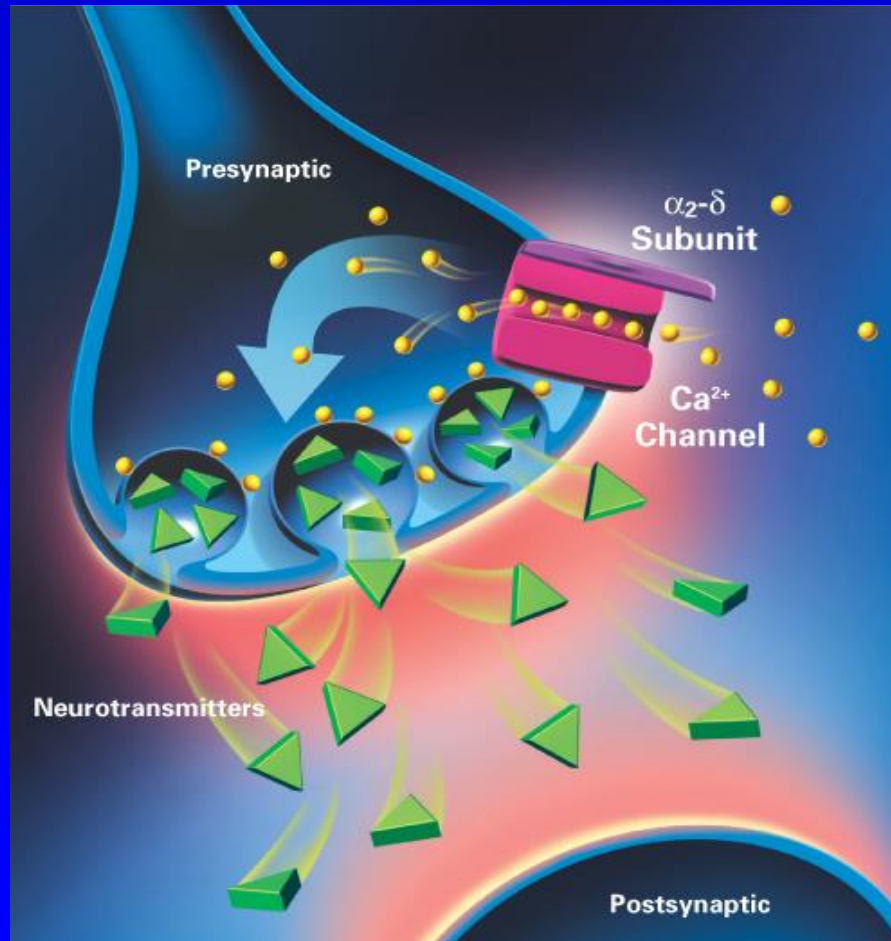


Max et al., N Engl J Med, 1992

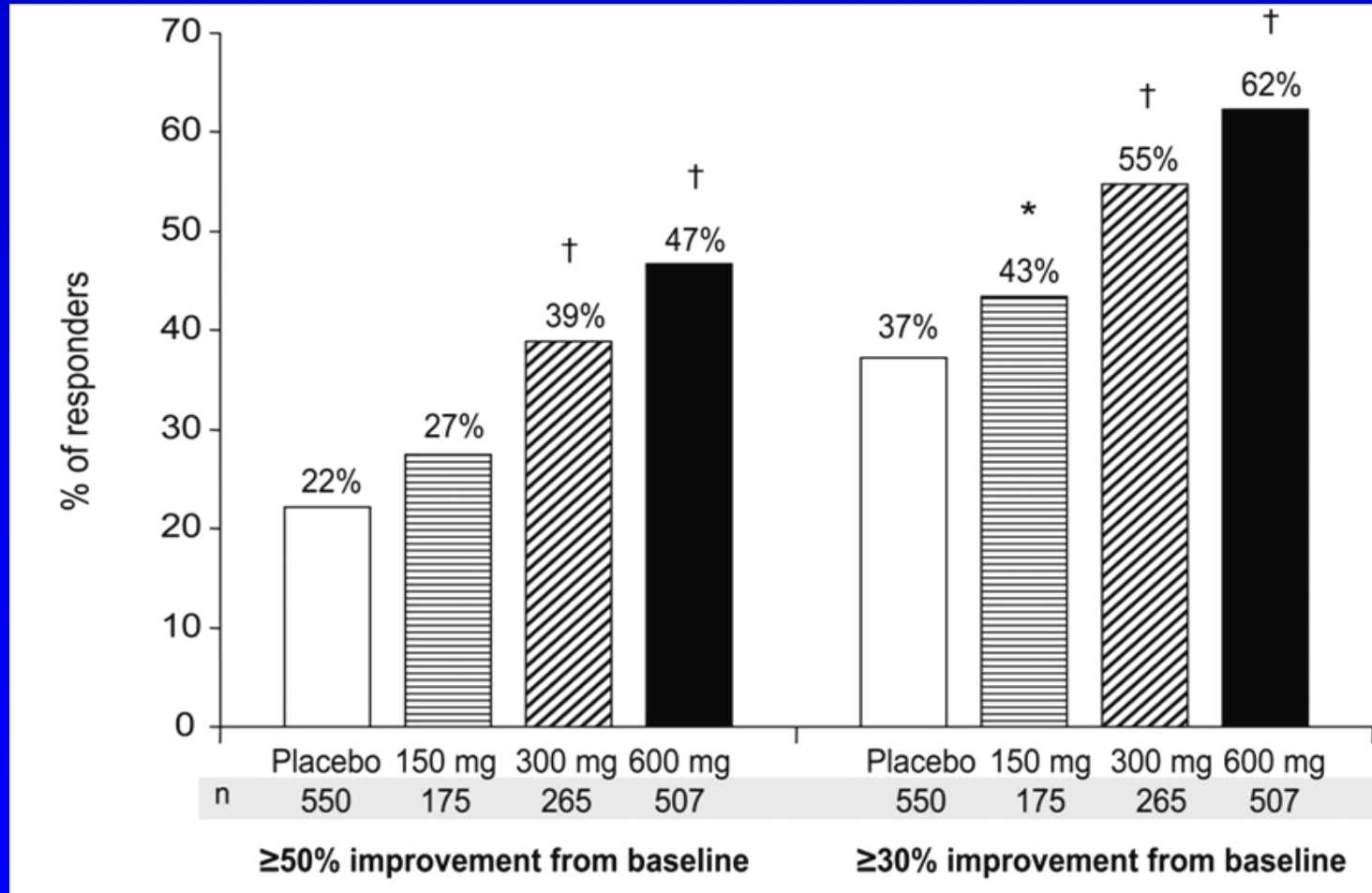
Gabapentin (114) Pregabalin

Hyperexcited neuron

Modulation of hyperexcited neuron with Pregabalin



$\geq 50\%$ and $\geq 30\%$ improvement

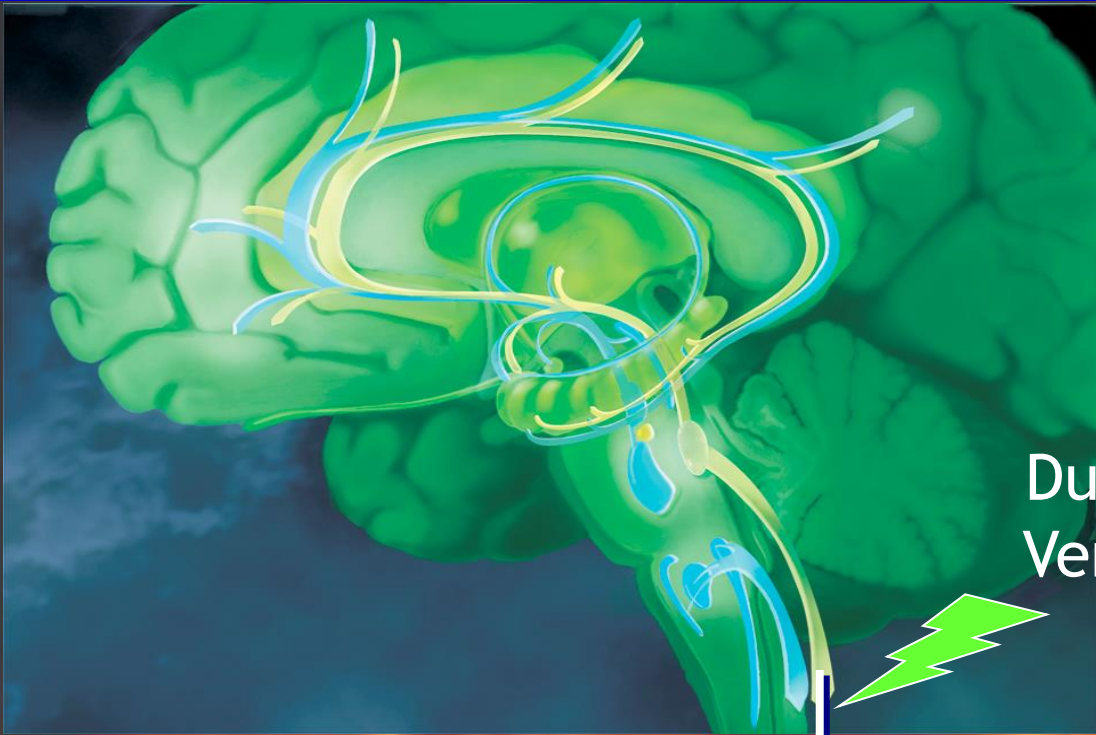


Freeman et al. *Diabetes Care* 2008; 31: 1448-54

Adverse events

	Placebo n=97 %	300mg/day n=81 %	600mg/day n=82 %
dizziness	5	27	39
somnolence	4	24	27
oedema	2	7	13
headache	10	9	10
amblyopia	1	5	9
ataxia	2	4	9
confusion	2	5	9
constipation	1	4	9





Duloxetine
Venlafaxine

SNRI

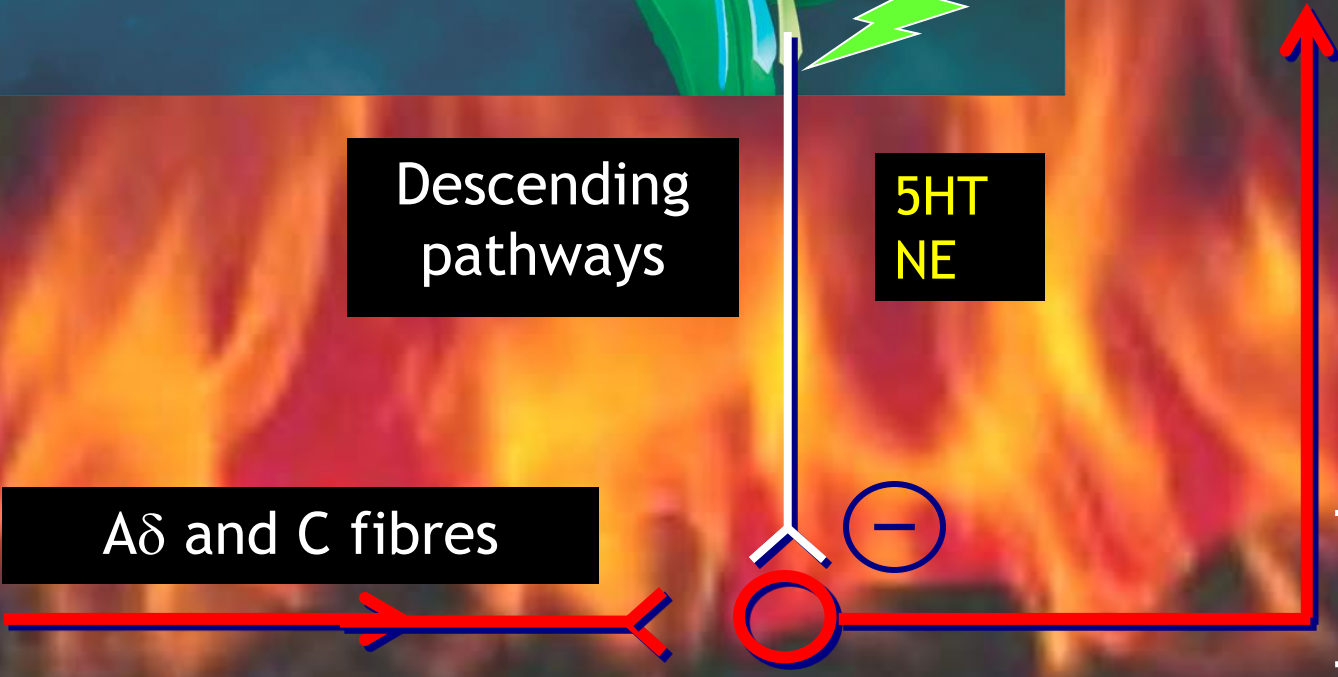
Descending pathways

5HT
NE

Ascending pathways

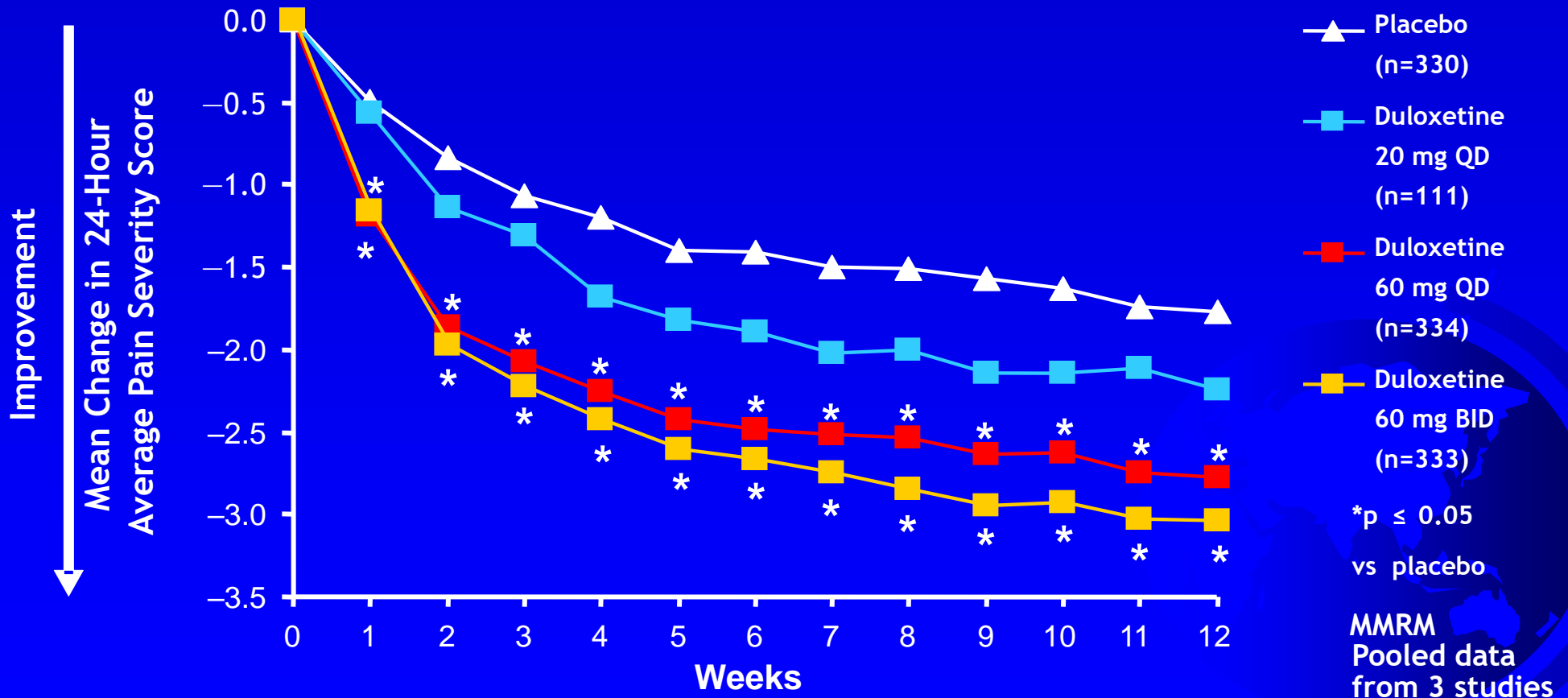
A δ and C fibres

Spinal cord



24-hour average pain

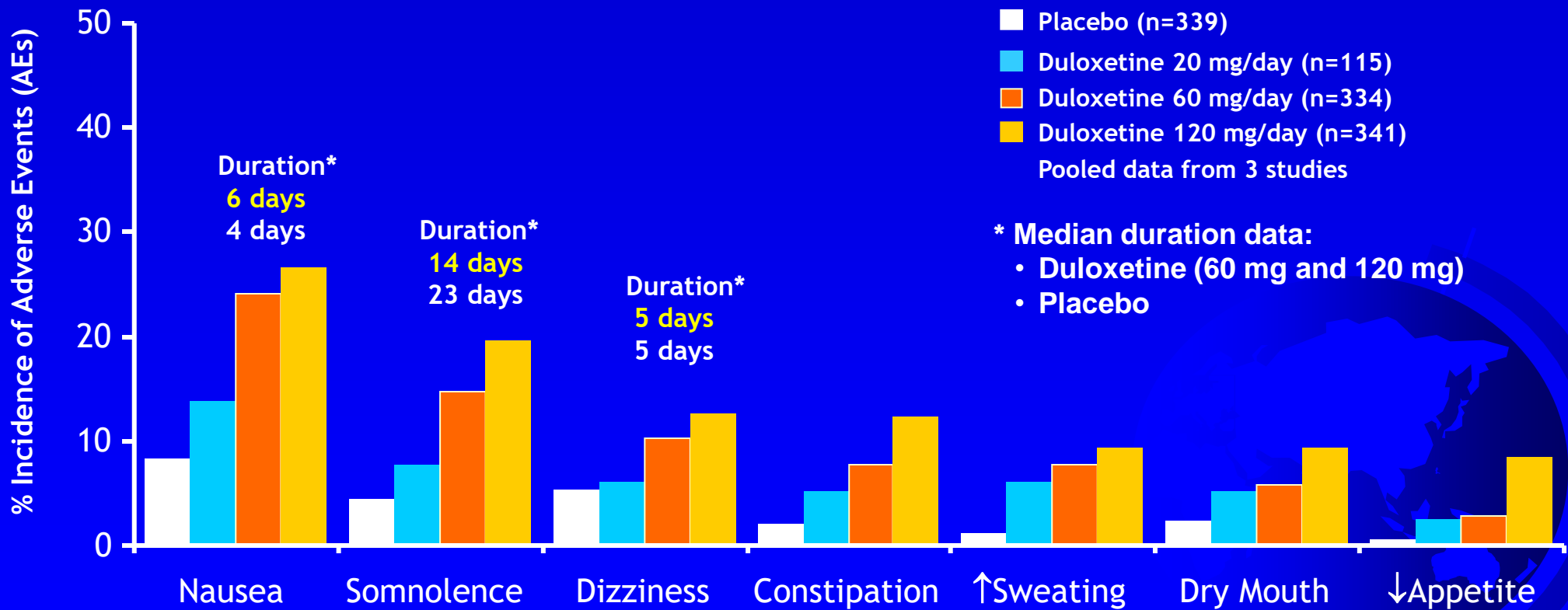
Mean baseline score 5.83



1. Robinson M, et al. Presented at: 8th International Conference on the Mechanisms and Treatment of Neuropathic Pain; 5 Nov 2005; San Francisco, CA, USA.

Adverse events

Duloxetine: Increased HbA1c and triglycerides NS



Head to Head comparisons?

Randomized, double-blind, placebo-controlled, parallel group or crossover clinical trials in DPNP:

Assessment: 5–13 weeks.

Efficacy criteria: Reduction in 24- hour pain severity.

Response rate ($\geq 50\%$ pain reduction)

Duloxetine (3),

Pregabalin (6), Gabapentin (2)

Amitriptyline (0).

Quilici et al. BMC Neurol 2009; 9: 1-14.



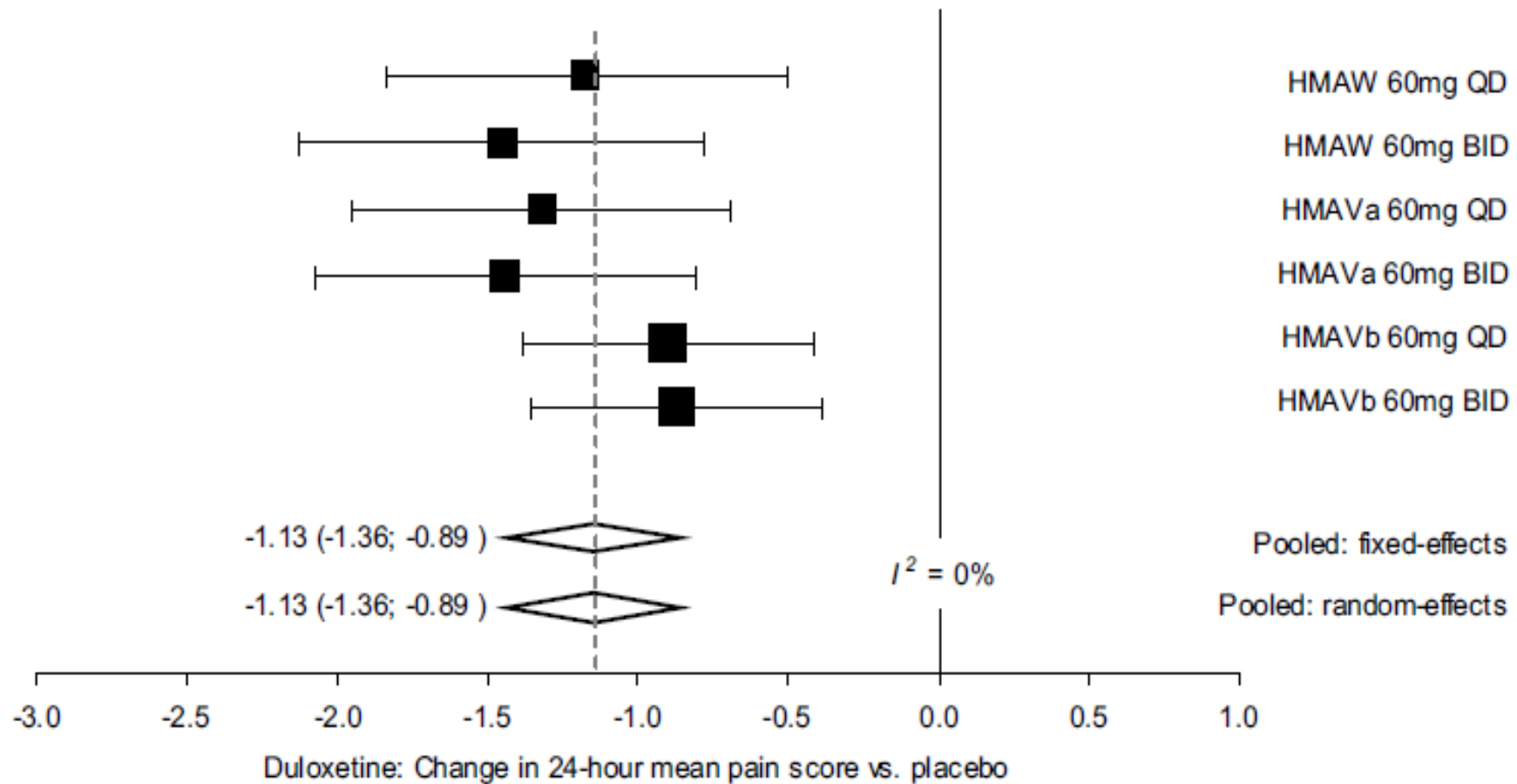
Meta-analyses

- Direct meta-analyses.
- Studies pooled by weighting the treatment differences by their inverse variances.
- Drug v Placebo
- NNT & NNH.



Metanalyses

Quilici et al. BMC Neurol 2009; 9: 1-14.



Pregabalin -0.89 NNT 5, NNH-19

Gabapentin -1.40- NNT ?, NNH-63

Duloxetine -1.13 NNT-5, NNH-11

Doctor's Pain Studies Were Fabricated.

New York Times March 10th

- ☞ Dr. Scott S. Reuben, anesthesiologist in Springfield, Mass. fabricated data in some or all of the 21 journal articles from 1996.
- ☞ The common practice — supported by his studies — of giving patients NSAID's and neuropathic pain medicines after surgery instead of narcotics is now being questioned.

(Raymond F. Kerins Jr., a Pfizer spokesman):

- ☞ “Independent clinical research advances disease treatments and improves the lives of patients, As part of such research, we count on independent researchers to be truthful and motivated by a desire to advance care for patients. It is very disappointing to learn about Dr. Scott Reuben's alleged actions.”

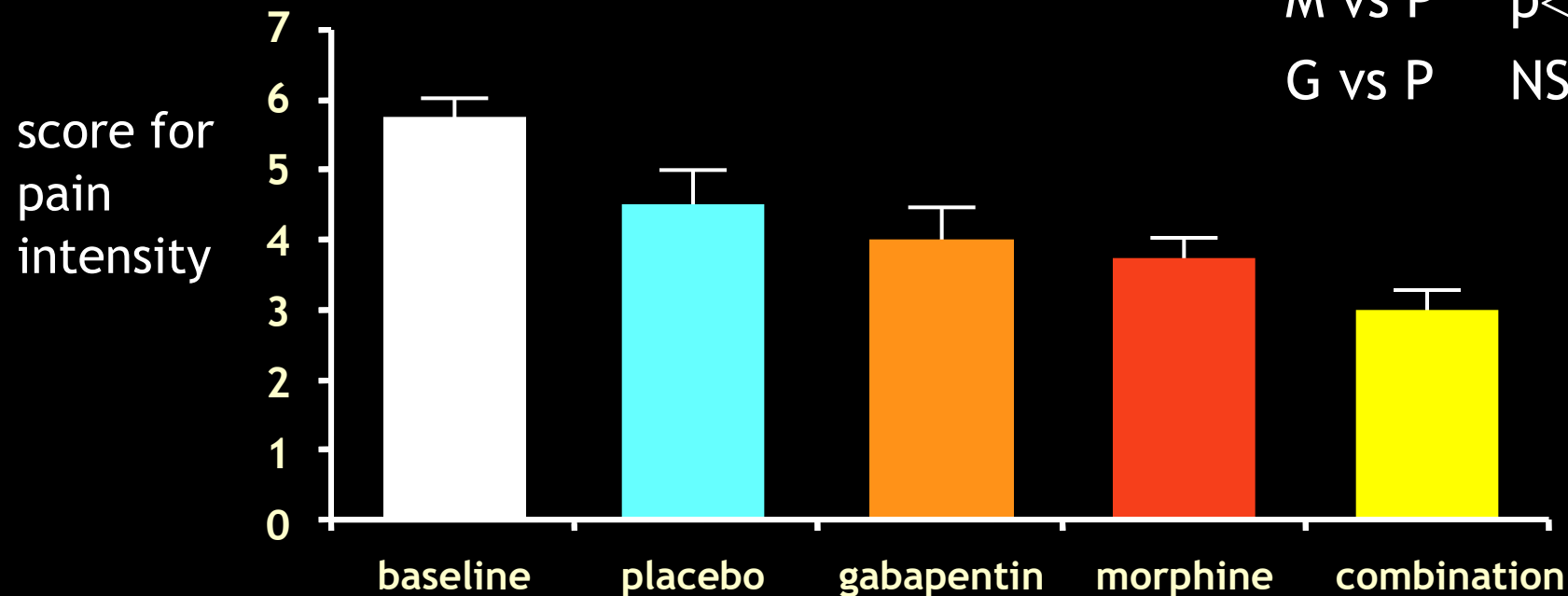
Combinations?



Morphine and Gabapentin treatment superior to either alone

57 (35 DM, 22 PHN) randomised;
41 completed

C vs G p<0.001
C vs M p<0.001
M vs P p<0.05
G vs P NS



Oxycodone + Gabapentin

- 338 patients with DPNP on maximum tolerated dose of gabapentin
- prolonged-release oxycodone v placebo added to therapy for up to 12 weeks

Results

- Oxy-gab reduced pain score by 33% from baseline
- Oxy-gab Vs placebo (P=0.007)
- Oxy-gab Vs gab (P=0.003)
- Oxy-gab associated with less escape medication use (P=0.03)

Davis et al. Eur J Pain. 2008;12(6):804-13



Alternatives



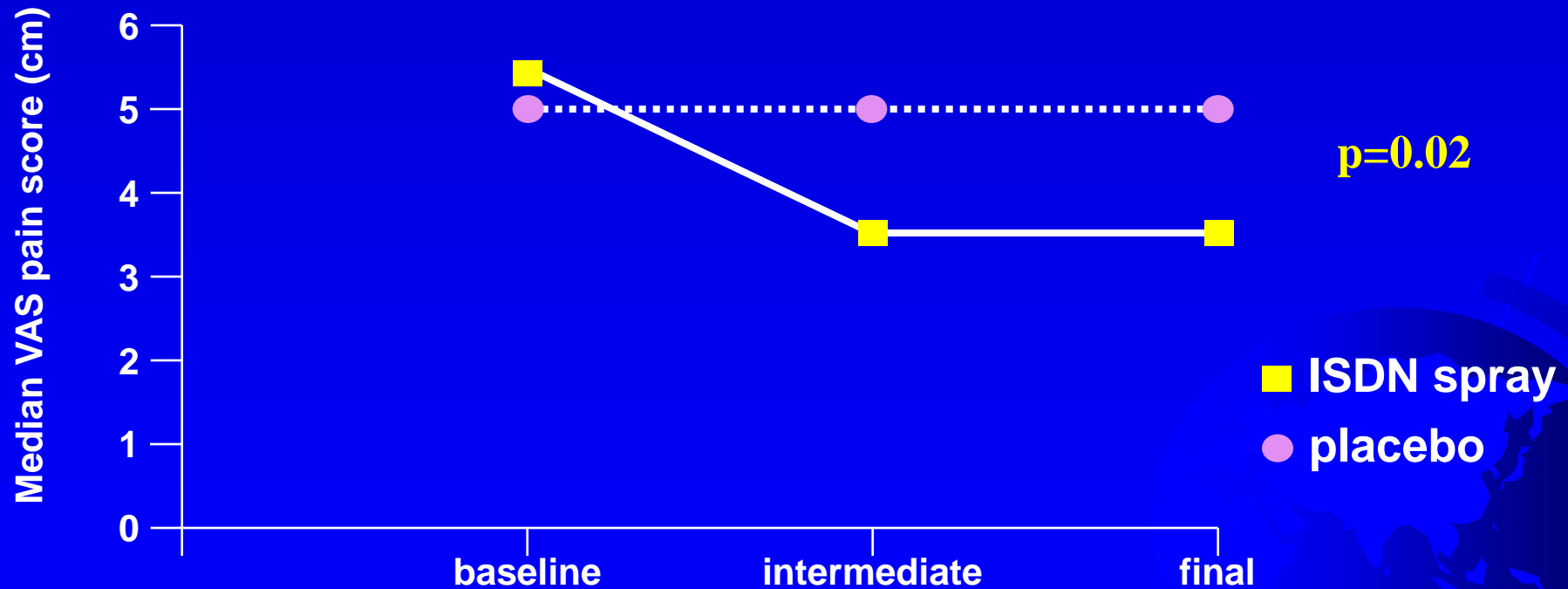
B Vitamins

- ✎ *Cochrane review 2008-MEDLINE (January 1966 to September 2005), EMBASE (January 1980 to September 2005).*
- ✎ *There are only limited data in randomised trials testing the efficacy of vitamin B for treating peripheral neuropathy and the evidence is insufficient to determine whether vitamin B is beneficial or harmful.*
- ✎ *Placebo effect*

Ang D et al. *Cochrane Database Syst Rev.* 2008 Jul 16;(3):CD004573.

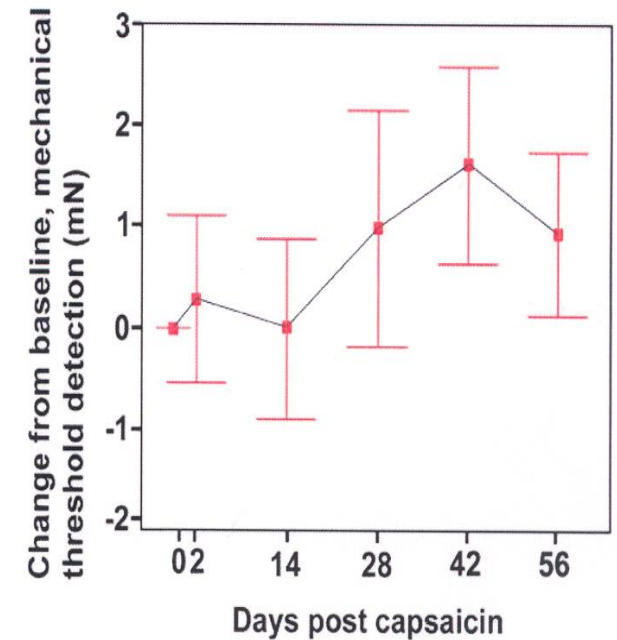
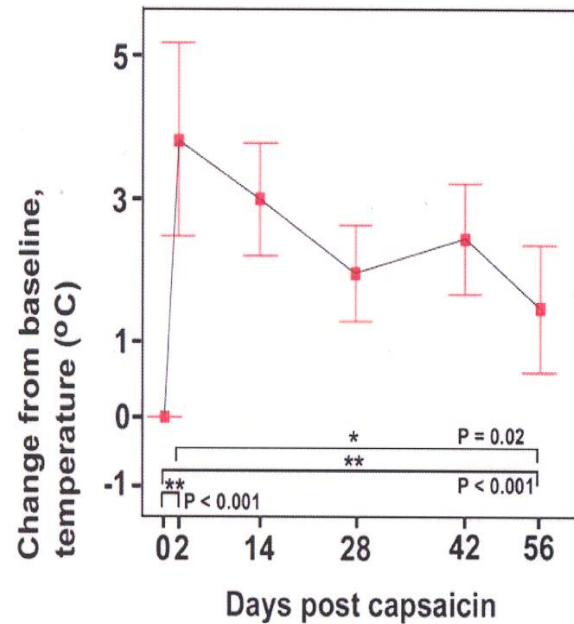
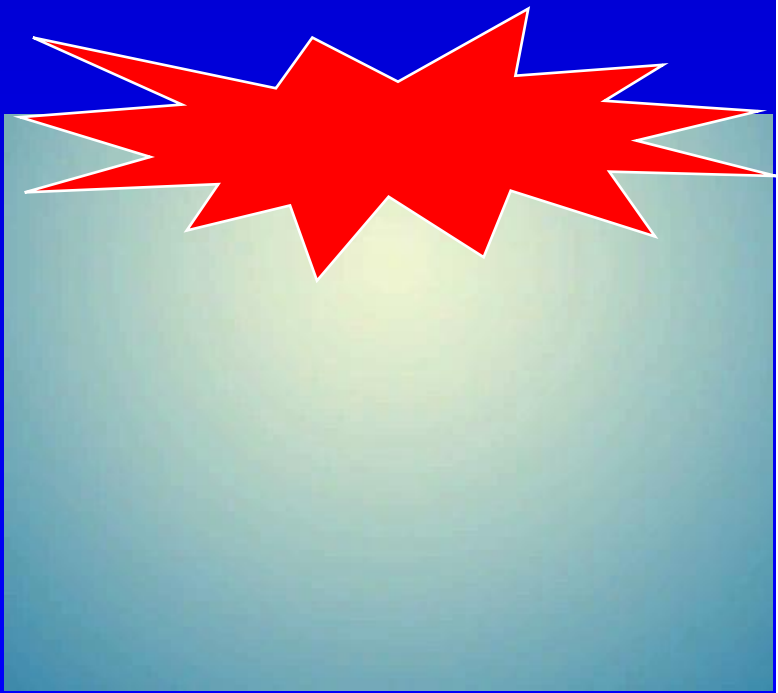
Isosorbide dinitrate spray

- n=22, duration of pain 2.6 ± 0.4 years
- randomised, placebo-controlled, cross-over design



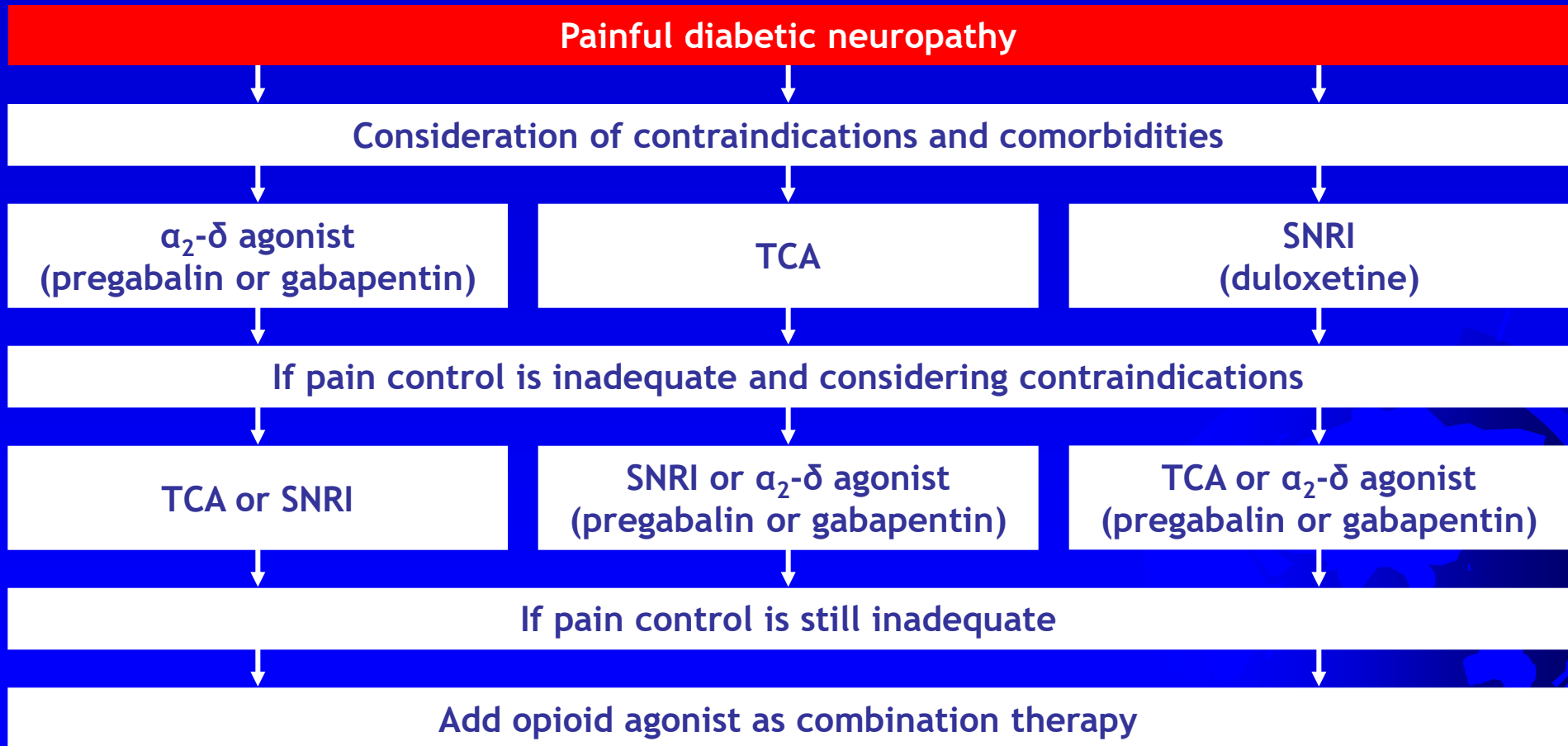
Yuen KC et al. Diabetes Care. 2002;25:1699-703.

Capsaicin!

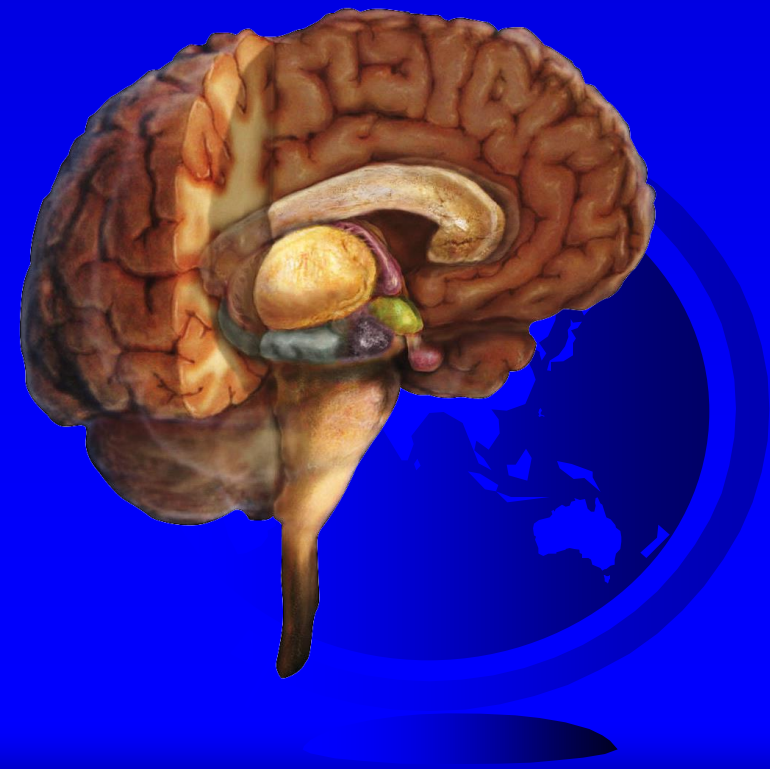


Polydefkis M et al. Neurology 2003

Treatment algorithm for DPNP



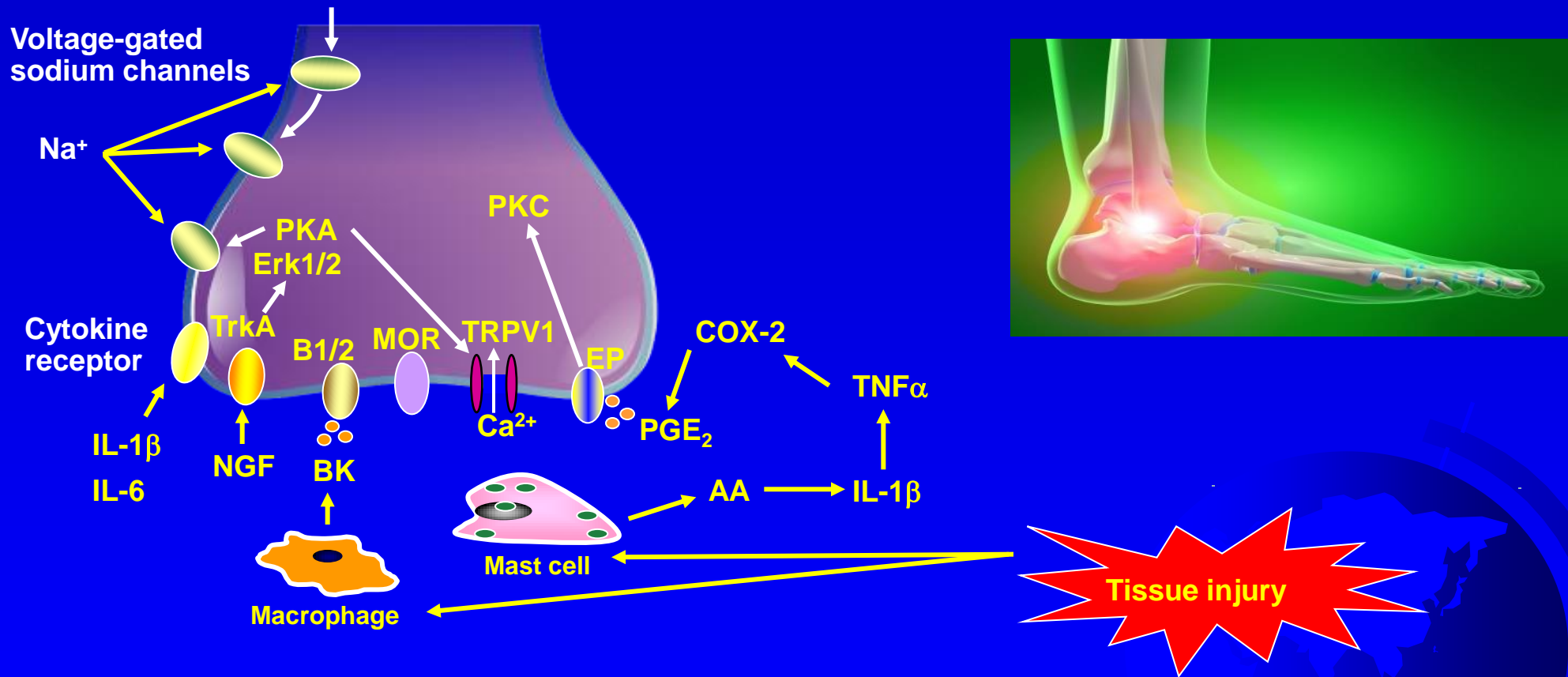
~1/3
Pain relief >50%?



Multiple Targets



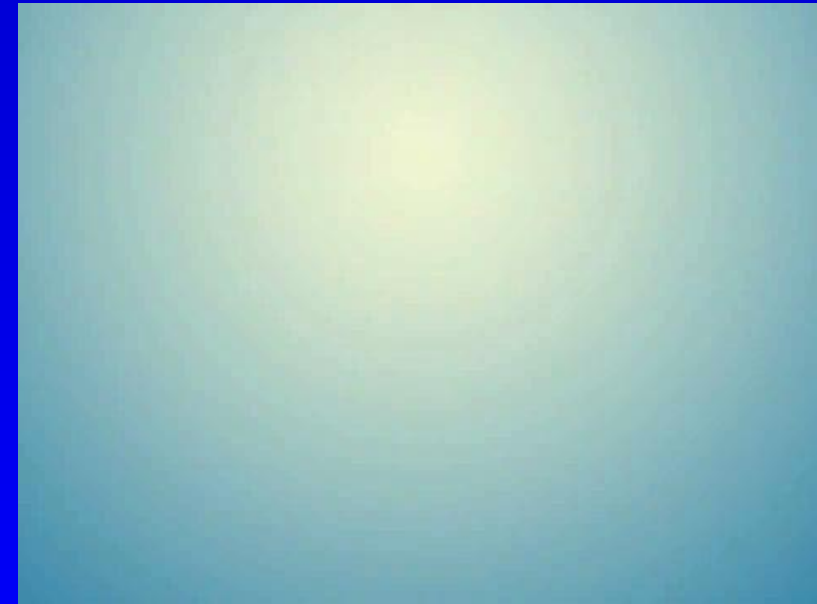
Novel drugs: Inflammatory soup



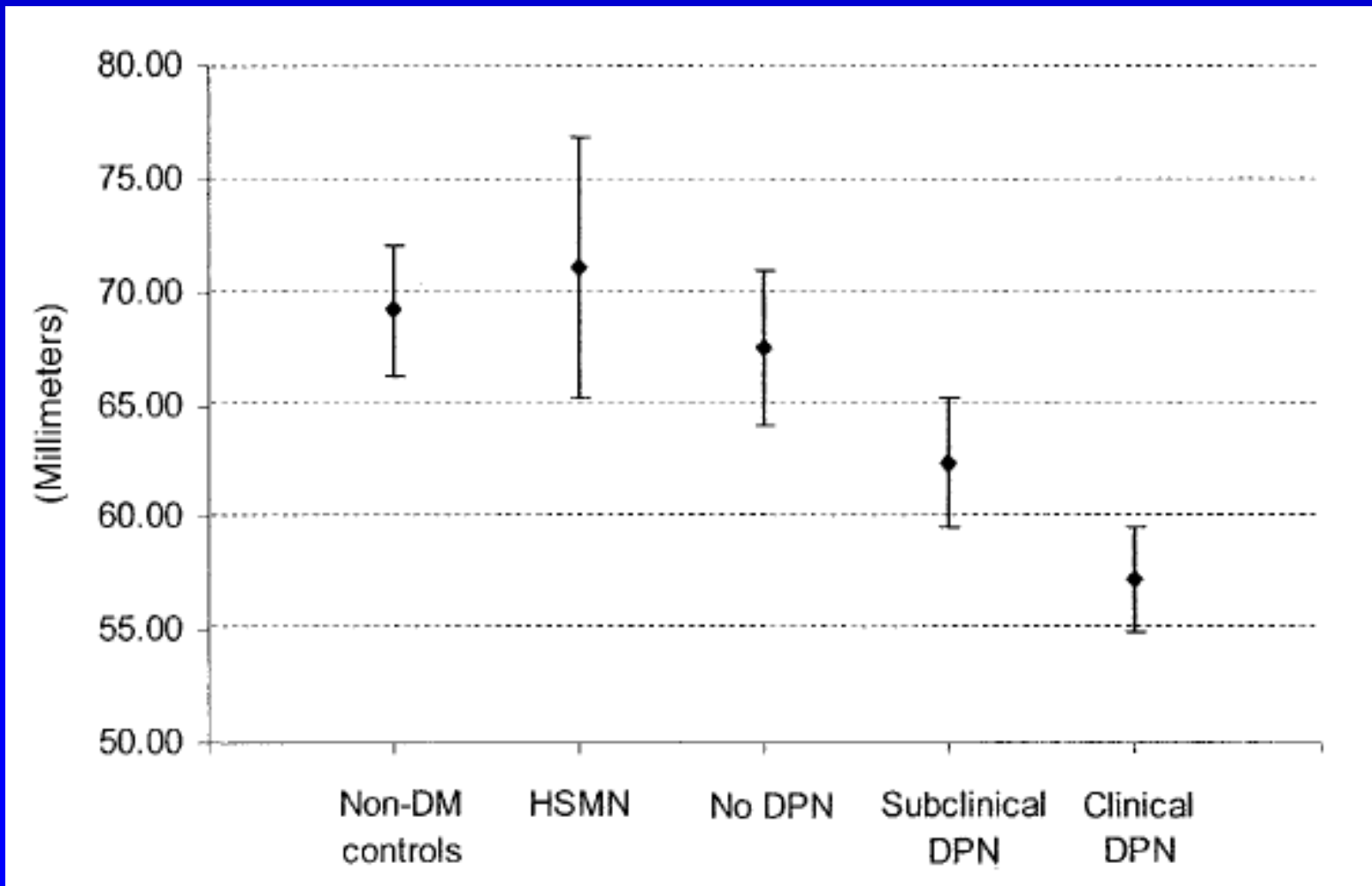
AA=arachidonic acid; BK=bradykinin; COX-2=cyclooxygenase-2; EP=prostaglandin E receptor; Erk1/2=extracellular signal-regulated kinases; IL=interleukin; MOR= μ opioid receptor; NGF=nerve growth factor; PGE₂=prostaglandin E₂; PKC, PKA=protein kinases C, A; TNF α =tumor necrosis factor alpha; TrkA=neurotrophic tyrosine kinase A receptor; TRPV1=transient receptor potential vanilloid 1

Novel Drugs

- Ranirestat (ARI)
- Dexlipotam (antioxidant)
 - Colenueramide (NGF)
 - TAK428 (NGF)
 - T2C003 (t2cure)
 - SB-509 (VEGF agonist)
 - SSR-180575 (Neuroregenerative)
 - AL-309 (Neurotrophic factor)

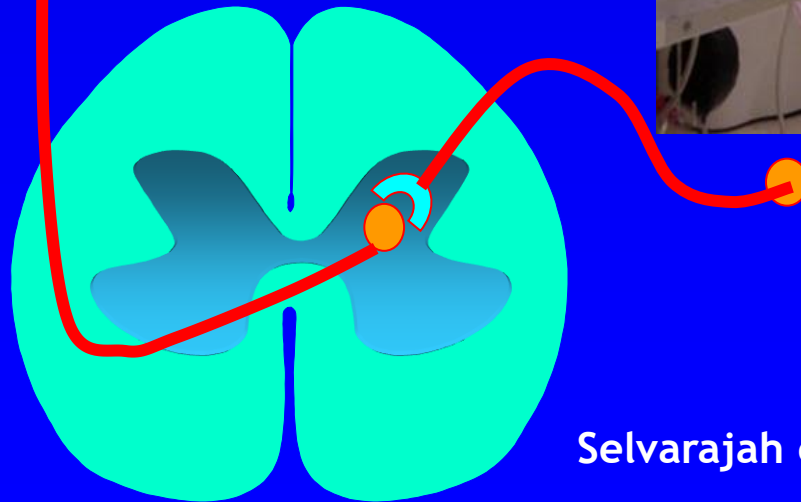
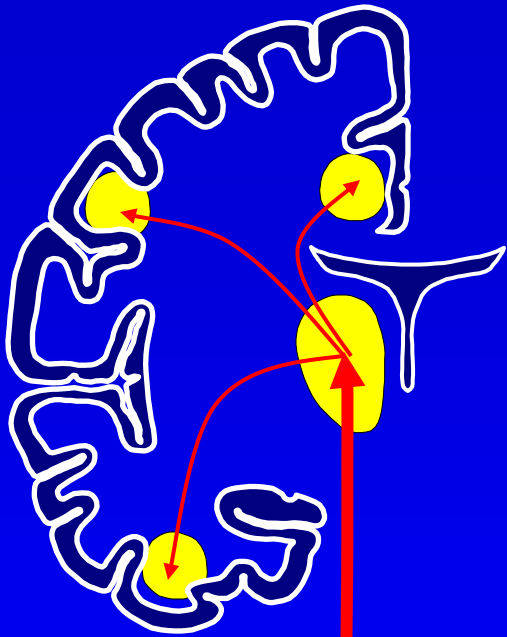


Spinal Cord



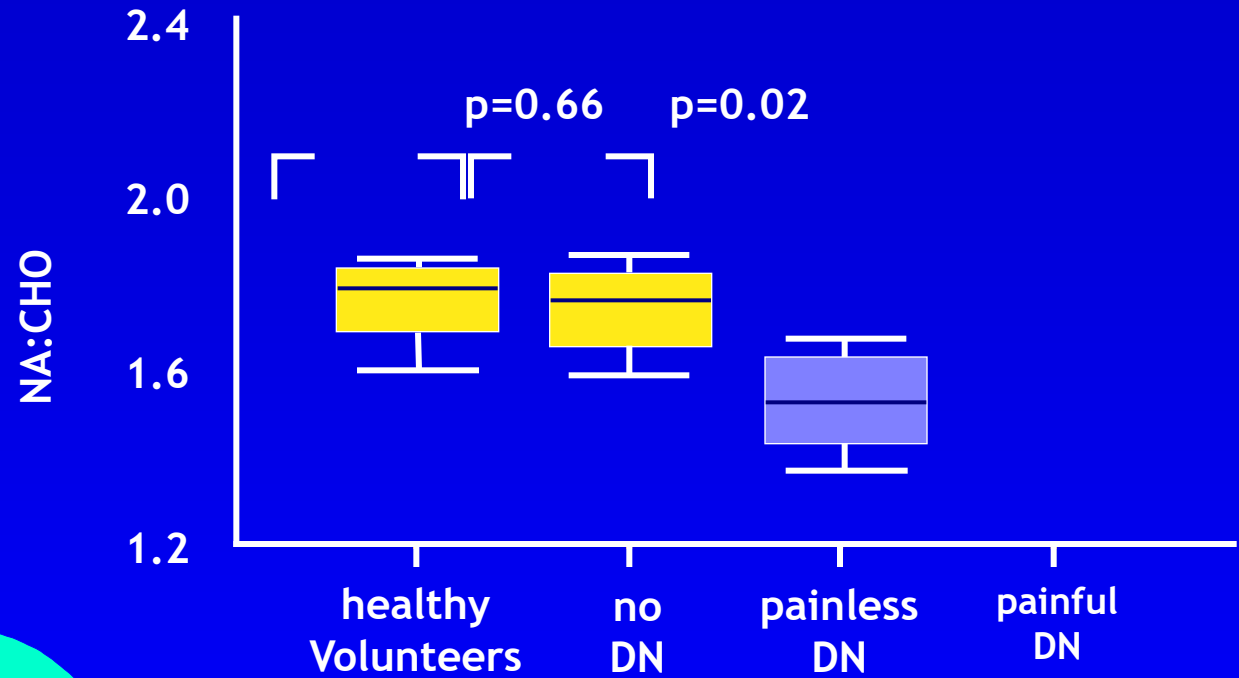
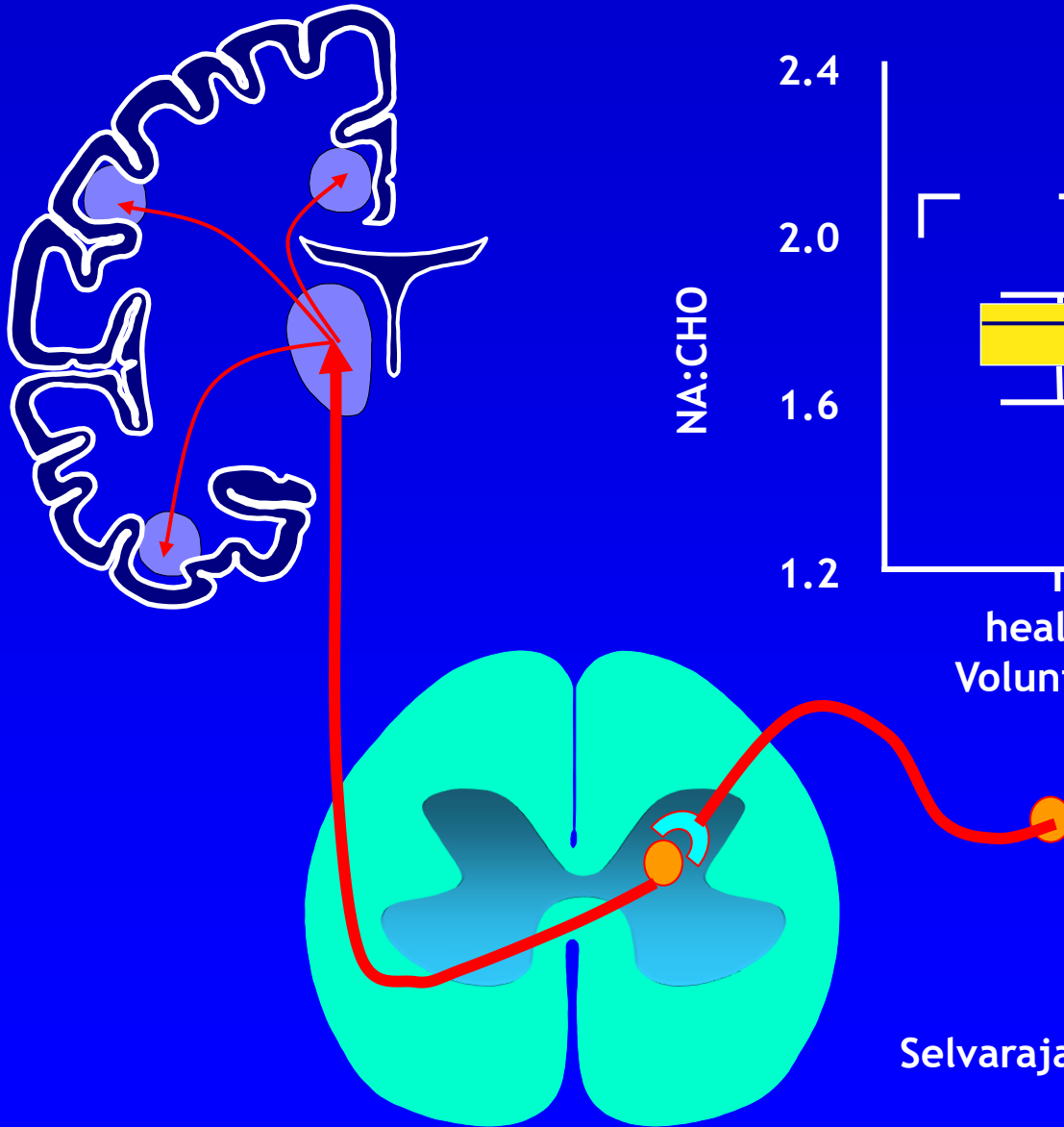
Selvarajah D, et al. *Diabetes Care*. 2006;29:2664–2669.

MR studies higher control

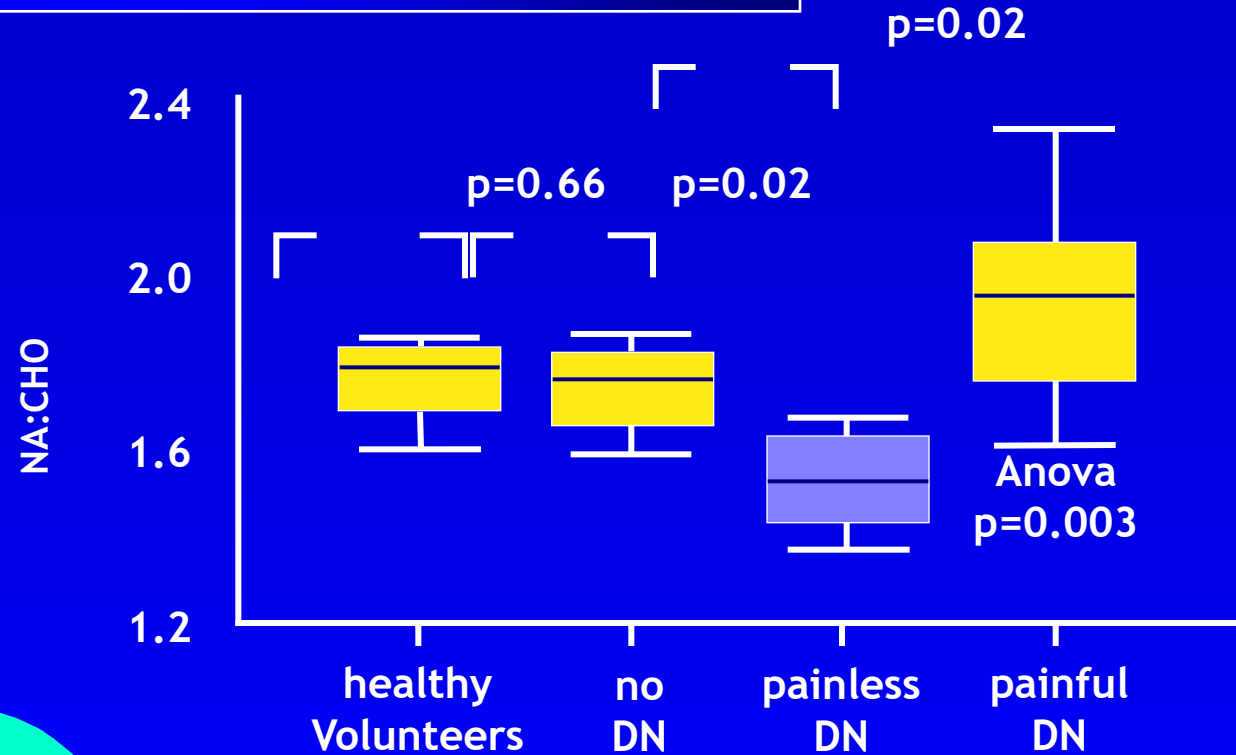
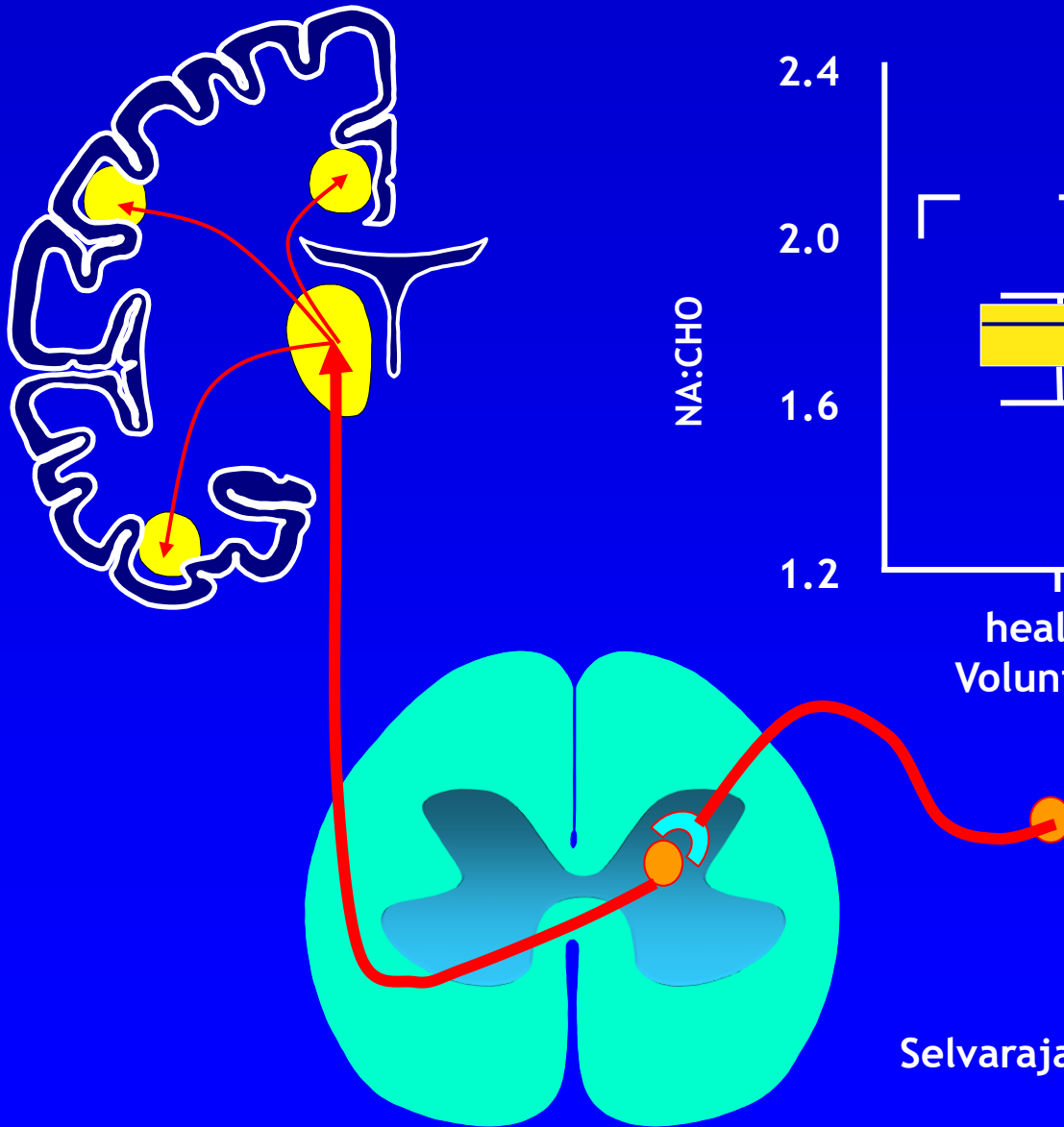


Selvarajah et al Diabetologia 2008 51(11):2088-92.

Thalamic dysfunction

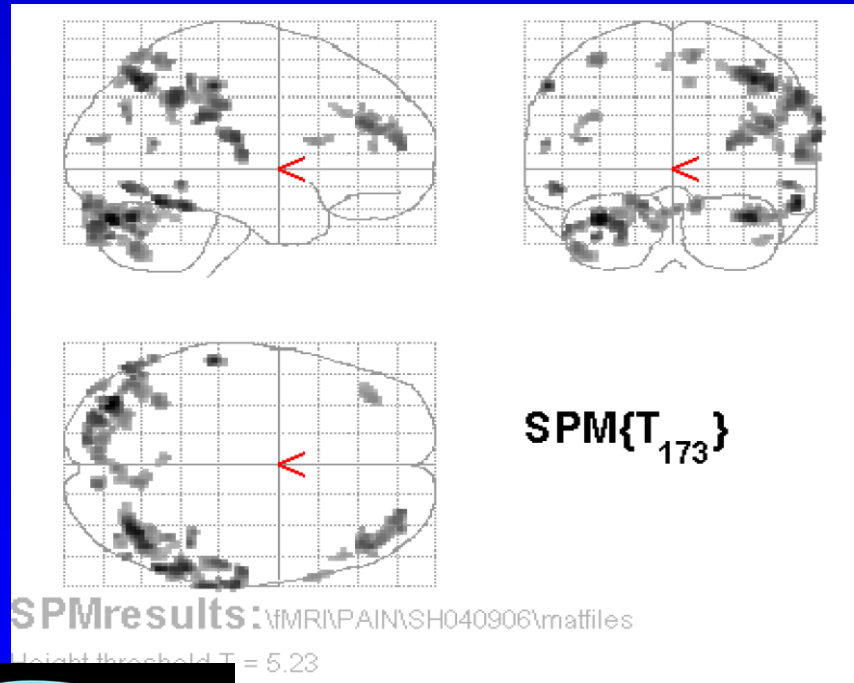


Thalamic dysfunction

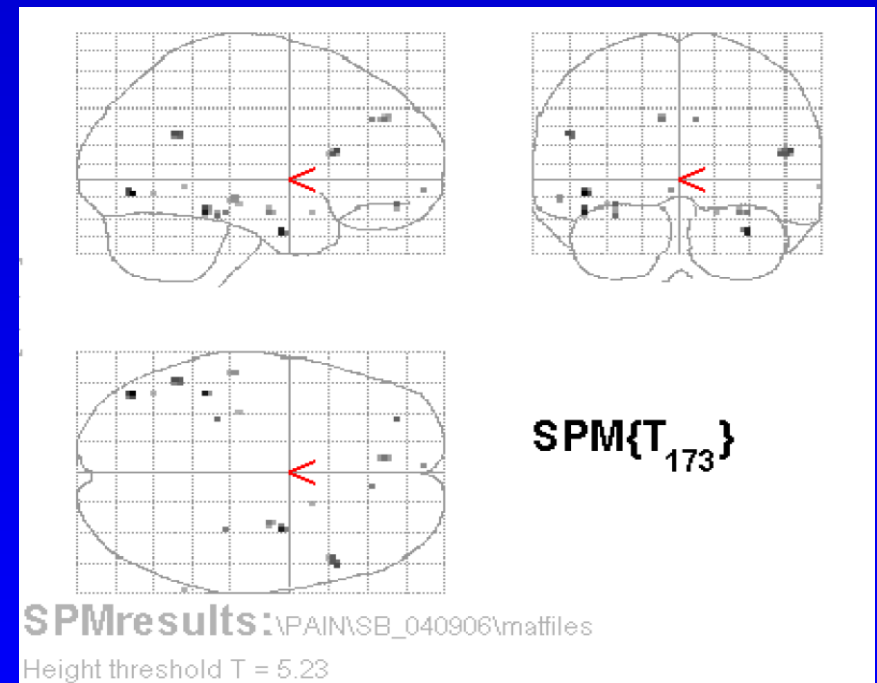


fMR studies

Painful-DPN



Painless-DPN



Neuropathic Pain: The future

Studies are required:

- ◆ On long-term analgesic efficacy.
- ◆ Head-to-head comparisons
- ◆ Use of drug combinations
- ◆ Targeted (multiple) treatment



Thank You.

