Teaching Course 12 : Neuropathic Pain-advice for clinical practice.

XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide
Santiago, Chile, October 31 - November 5, 2015
WCN 2015

CENTRO DE DOR
DO DEPARTAMENTO DE
NEUROLOGIA DA FMUSP

Evidence-based pharmacological treatments

Pr. Daniel Ciampi de Andrade

Centro de Dor, Departamento de Neurologia, Universidade de São Paulo, Brasil

Instituto do Câncer do Estado de São Paulo, Brasil

ciampi@usp.br

Disclosure Slide

1. I participated in board meetings for Pfizer, Grunenthal, Medtronic, Mundipharma.
2. I have been involved in "investigator initiated research" trials with Pfizer, Mundipharma, Meizler-UCI, and Saint-Jude Medical.

Learning objectives

During this presentation, the following topics will covered:

1. The role of pharmacological interventions in the treatment of NeP;

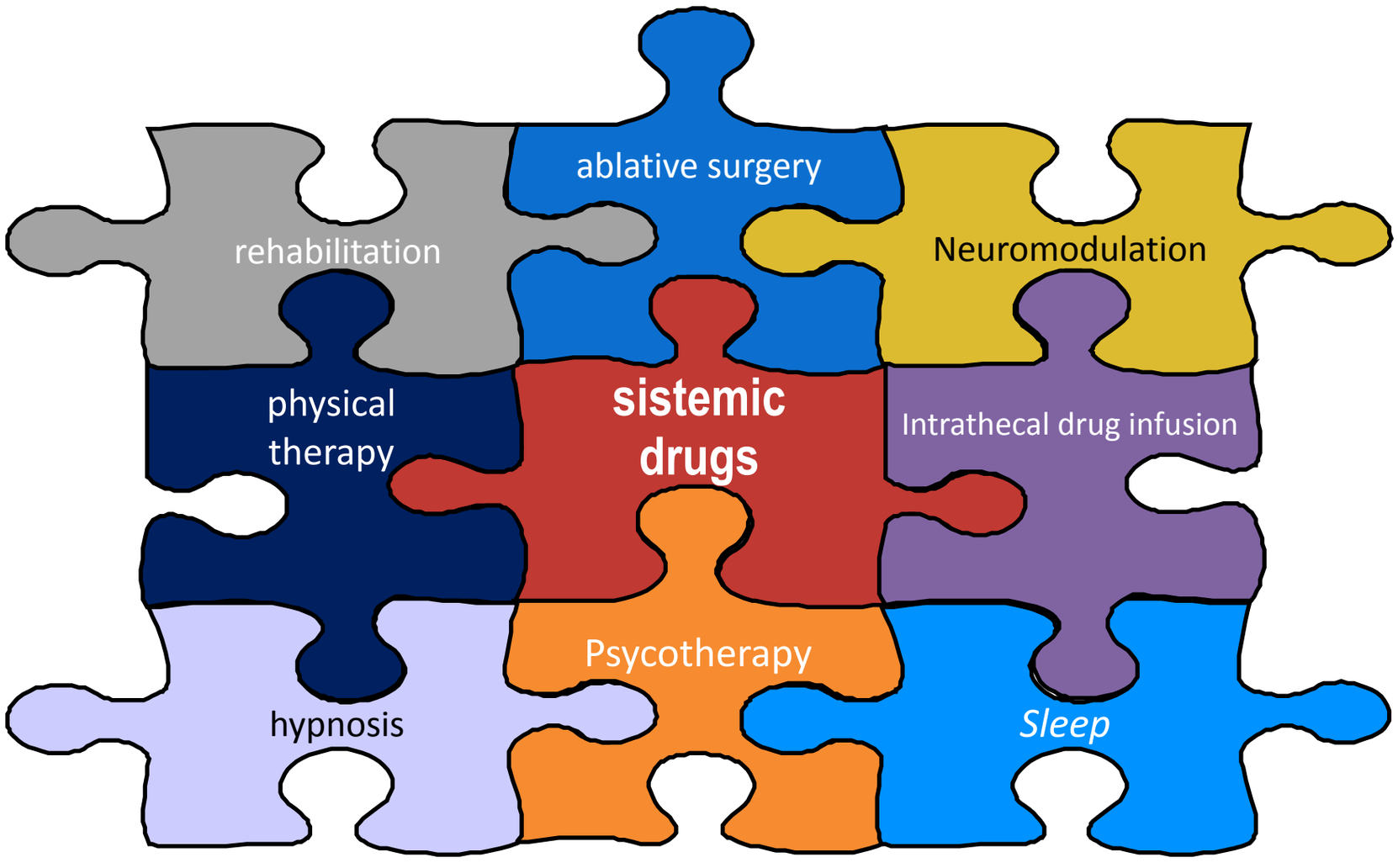
2. The basic pharmacological properties of the main drugs used to treat NeP;

3. The actual efficacy of drugs used to treat NeP and their propensity to cause adverse events

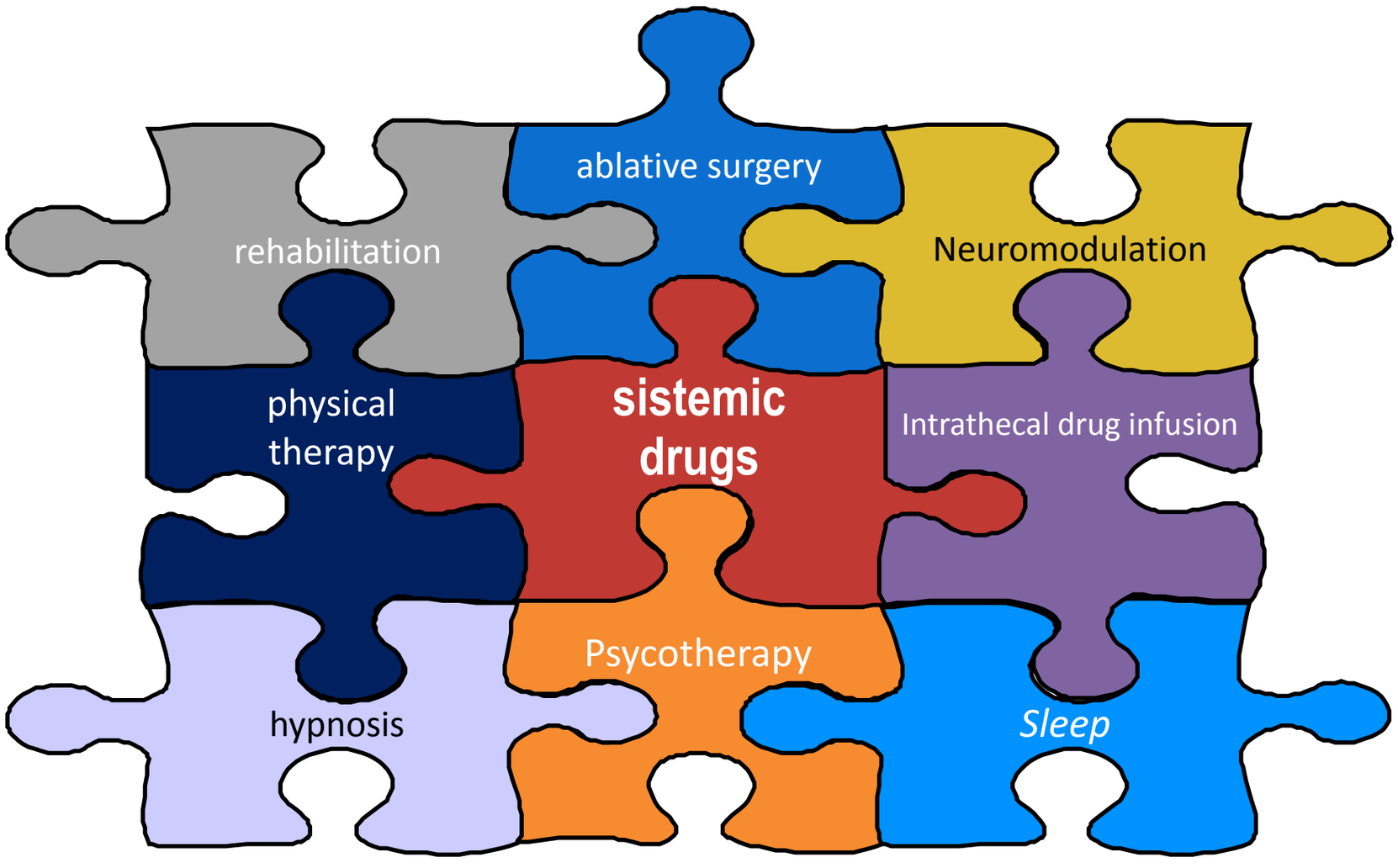
4. The basis of combination therapy for NeP;

5. The limitations of the current evidence-based treatments for NeP and the rationale of mechanism-based approach to NeP.

Treatment of Neuropathic Pain



Treatment of Neuropathic Pain



ATTENTION:

Evidence-based treatment *vs*. individualized treatment

Positive evidence ≠ negative evidence ≠ insufficient evidence

The size of the problem - Pharmacological treatment of NeP

Response has been defined as a 30-50% decrease in pain intensity compared to placebo

55% of trials were performed in DPP and PHN

Very low number of studies were performed in other etiologies of NeP such as central pain, HIV associated pain, chemo-associated NeP

Up to 40% of patients with neuropathic pain (NeP) are pharmaco-resistant [Hansson 2009].

Most studies assessed the effects of drugs as monotherapy. [Finnerup et al., 2015]

Combination treatment has been assessed in 11% of the trials.

There is no correlation between etiology of neuropathic pain and its symptoms (mechanisms) or treatment response. [Attal 2008]

Main classes of drugs used in NeP

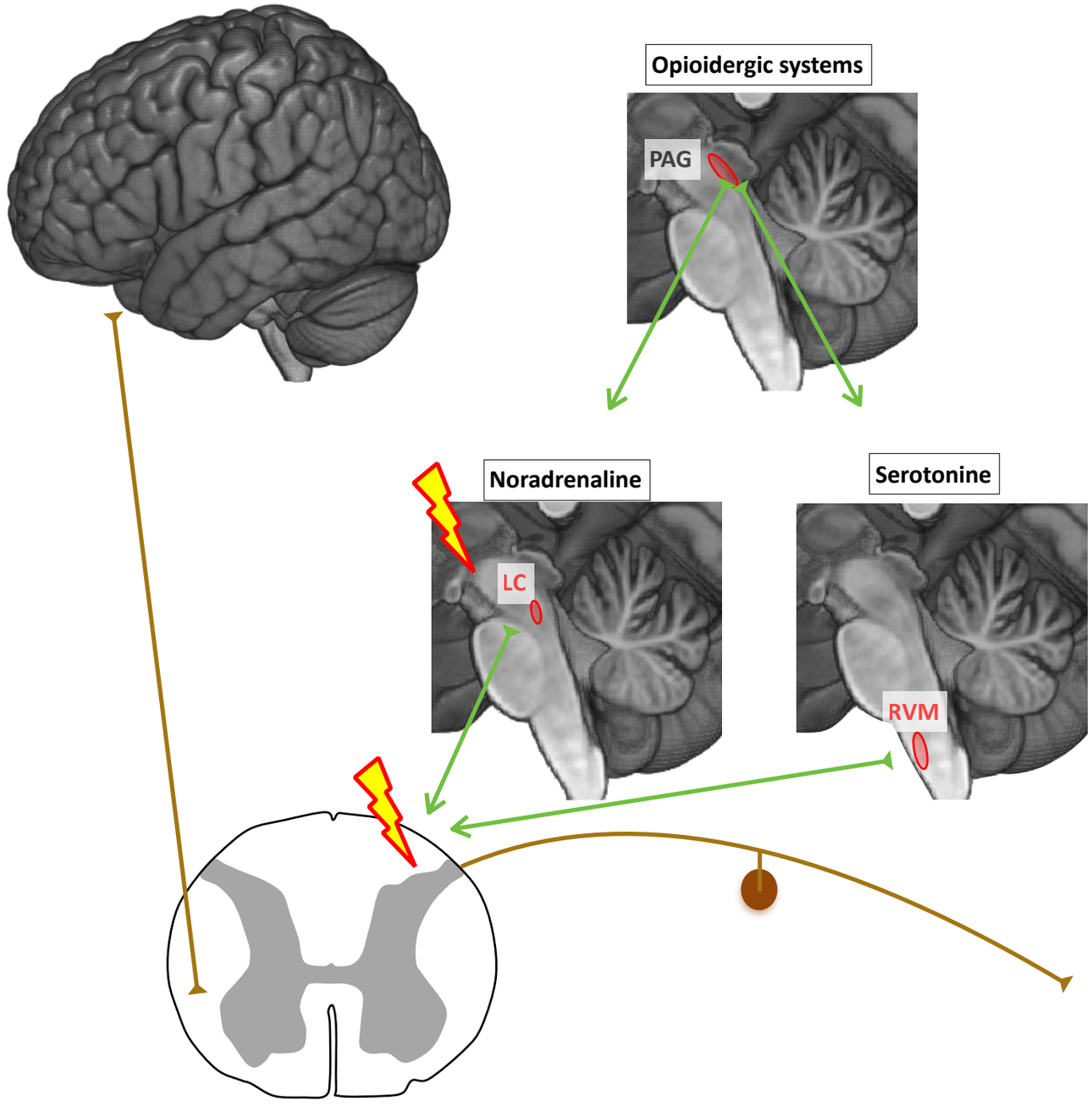
1. α2δ - ligants (“gabapentinoids")

Pregabalin
[150-600 mg/d (2xday)]

+Acts on a subunit of primary afferent Ca channel decreasing neuronal hyper sensitivity and increases the action of descending noradrenergic inhibitory control; +Not metabolized
+Excretion in urine (97%)
+Time to analgesia onset: days
+Main adverse events: dizziness, leg edema, mental changes, weight gain
+Serious adverse events: skin reactions
+Contraindications: none
+Pregnancy C

Gabapentin
[900-3600 mg/d (3xday)]

+Acts on a subunit of primary afferent Ca channel decreasing neuronal hyper sensitivity and increases the action of descending noradrenergic inhibitory control;
+Not metabolized
+Excretion in urine (97%)
+Time to analgesia onset: days
+Main adverse events: dizziness, leg edema, mental changes, weight gain
+Serious adverse events: skin reactions
+Contraindications: none
+ Pregnancy C



Main classes of drugs used in NeP

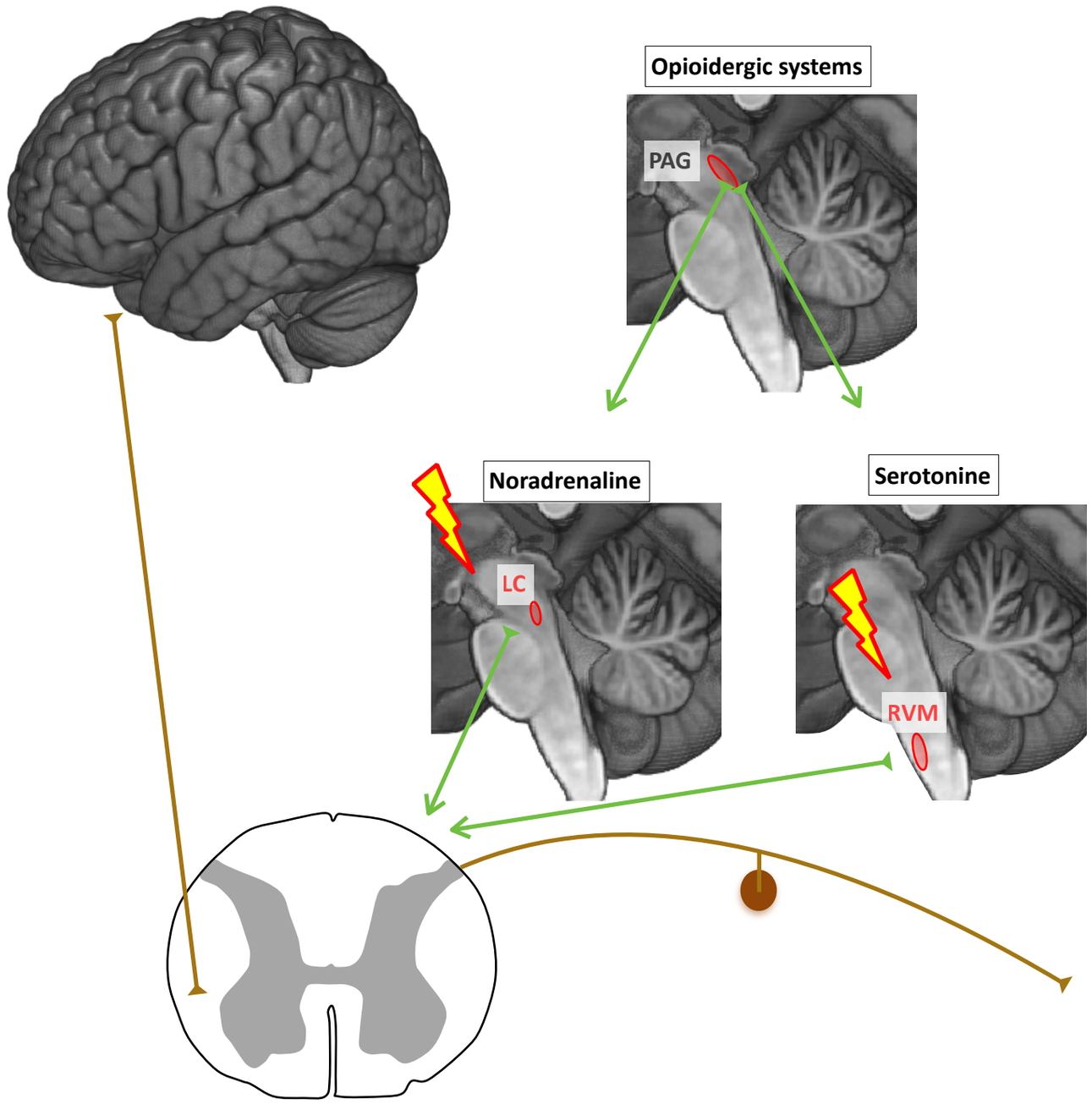
2. Serotonin and Noradrenalin Reuptake Inhibitors (SNRI's)

Duloxetine
[60-120 mg/d (once a day)]

+Acts increasing the availability of NE and 5-HT increasing descending inhibitory control;
+Metabolized by CYP-2D6
+Time to analgesia onset: weeks
+Main adverse events: dizziness, nausea, sweating, sexual dysfunction mental changes, weight loss.
+Excretion: urine 70%
+ Contraindications: hepatic or renal failure
+ Pregnancy C

Venlafaxine
[150-225 mg/d (once a day)]

+Acts on a subunit of primary afferent Ca channel decreasing neuronal hyper sensitivity and increases the action of descending noradrenergic inhibitory control;
+Excretion: urine 87%
+Metabolized by CYP-2D6
+Time to analgesia onset: weeks
+main adverse events: dizziness, nausea, sweating, sexual dysfunction mental changes, weight loss, hypertension
+Contraindications: hepatic or renal failure
+ Pregnancy C

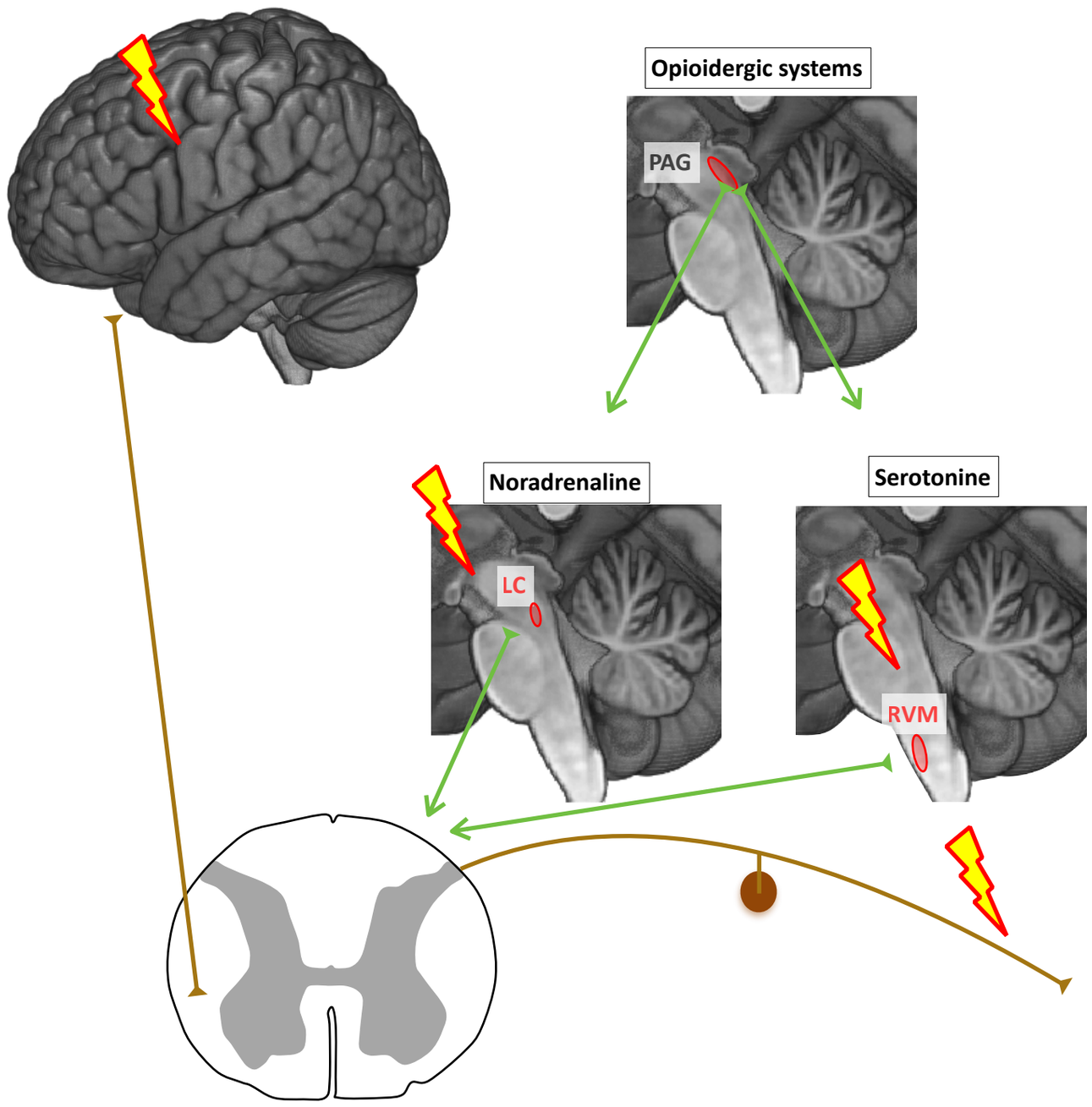


Main classes of drugs used in NeP

3. Tricyclics Antidepressants (TCA's)

Amtriptyline, Nortriptyline, Imipramine, Chlomipramine, Maprotiline
[25-150 mg/d (once a day)]

+Act increasing the availability of NE and 5-HT increasing descending inhibitory control;
+ Anticholinergic, antihistaminergic, Na channel blocker
+Metabolized by CYP-1A2, 3A4, 2D6
+time to analgesia onset: weeks
+main adverse events: wight gain, somnolence, dizziness, orthostatic hypotension, xerostomia, constipation
+Excretion: urine 70%
+ Contraindications: acute MI, narrow angle glaucoma, AV-block
+ Pregnancy C-D

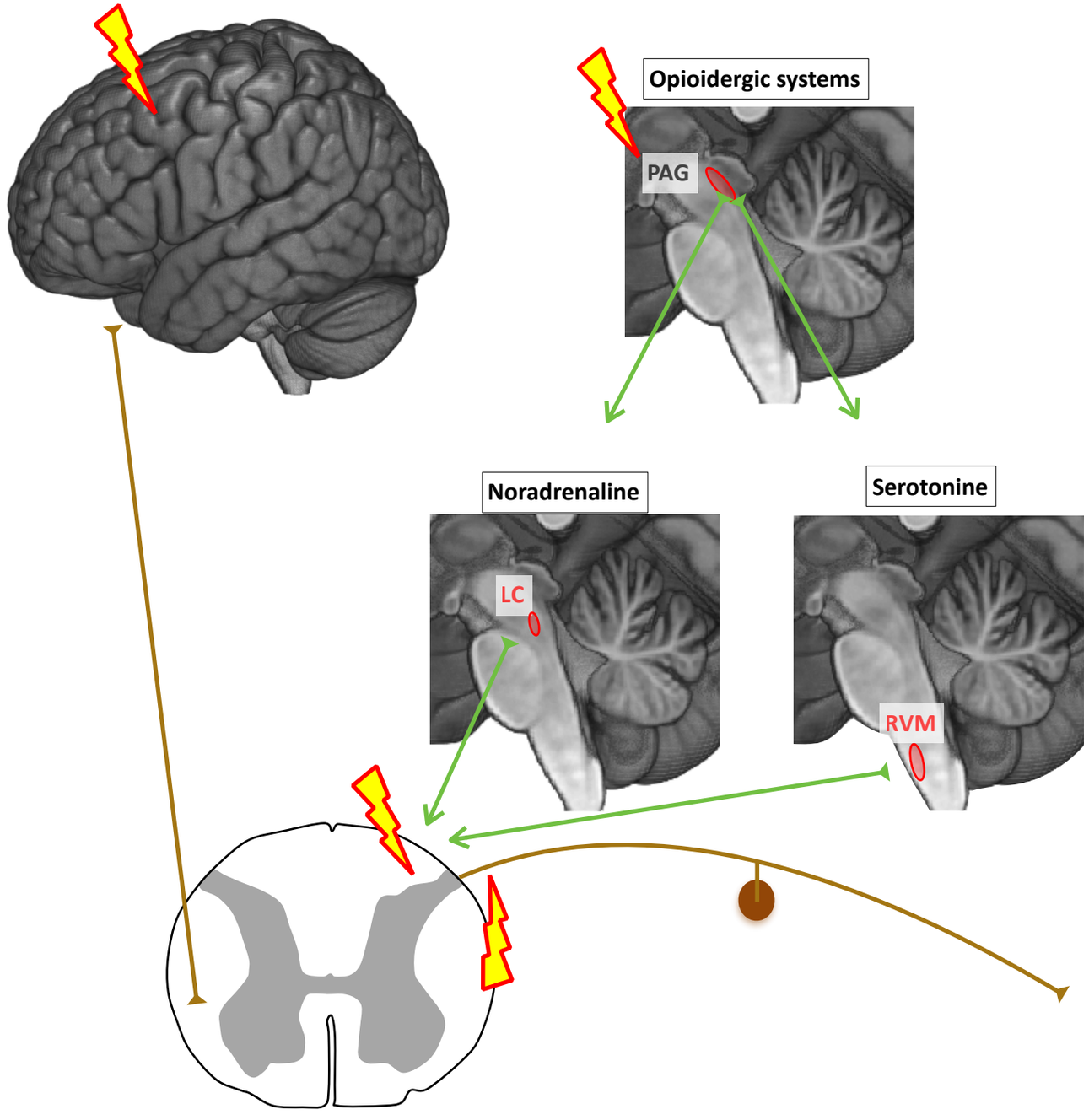


Main classes of drugs used in NeP

4. Opioids

Oxycodone
[20-120 mg/d (2-3xday)]
Tramadol
[150-400 mg/d (3xday)]
Morphine
[30-… mg/d (4xday)]
Metadone
[10-480 mg/d (2-3xday)]

+Acts on descending inhibitory control; acts on pre- and post-synaptic neurons, acts centrally in cortical areas with high concentration of opioid receptors (ACC, Insula, Amygdala)
+Not metabolized
+Excretion in urine (97%)
+Time to analgesia onset: hours
+Main adverse events: dizziness, mental changes, constipation
+Serious adverse events: respiratory depression, urinary retention, tolerance, abuse
+Pregnancy C



Main classes of drugs used in NeP

5. Other drugs

Botulinum Toxin A
[100-200 UI every 3 months

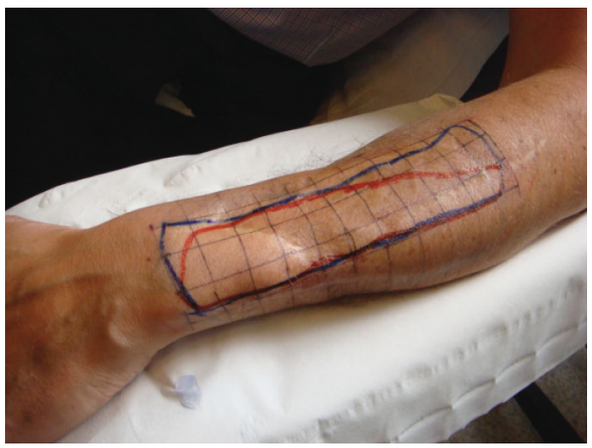
Lidocaine 5% patch
[up to 3 patches up to 12 hours a day]

Capsaicin 8% patch
[1-4 patches every 3 months]

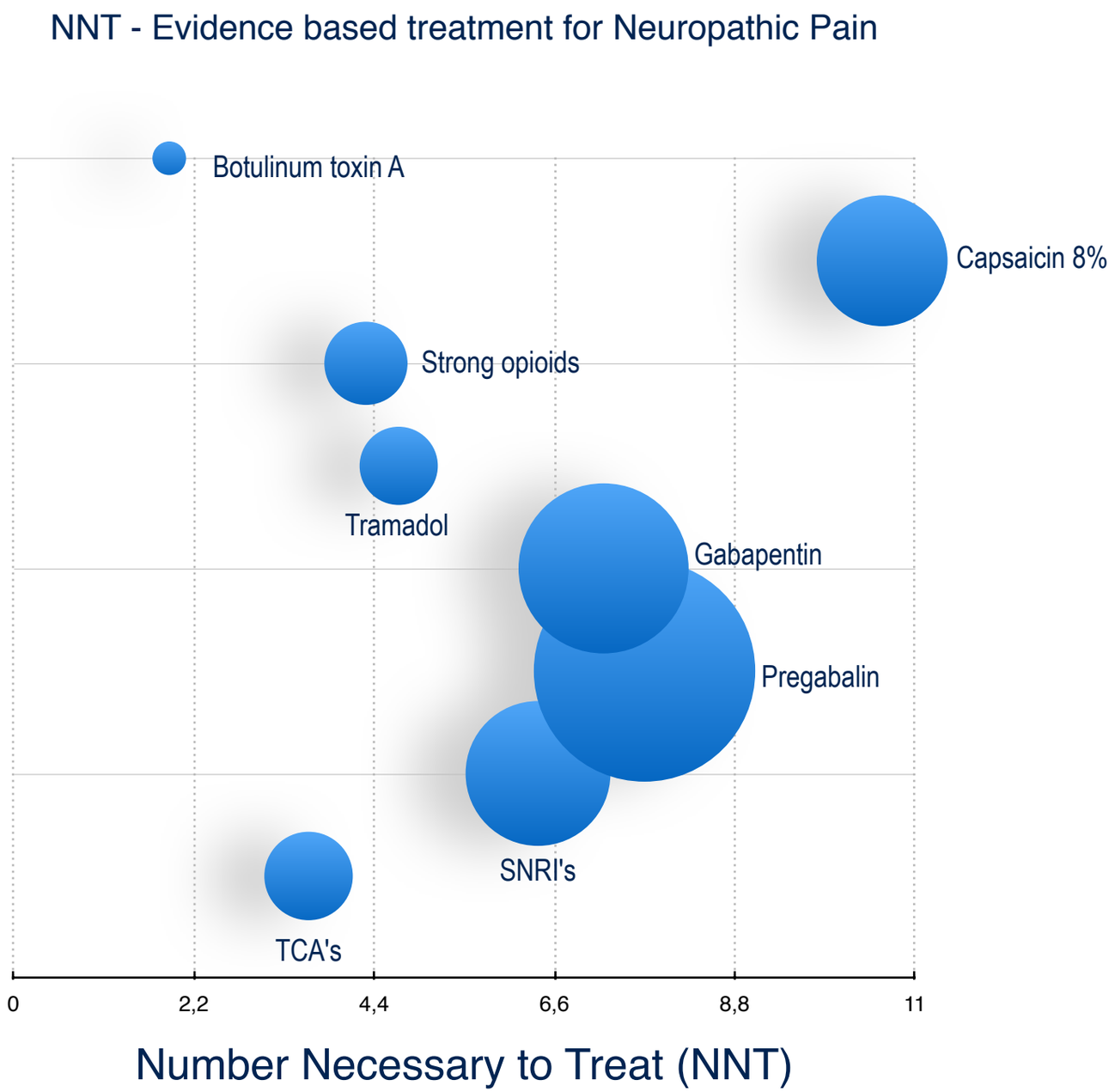
Lamotrigine
[200-400mg/d]

Carbamazepine
[400-1200mg/d]

Oxcarbazepine
[600-1800mg/d]

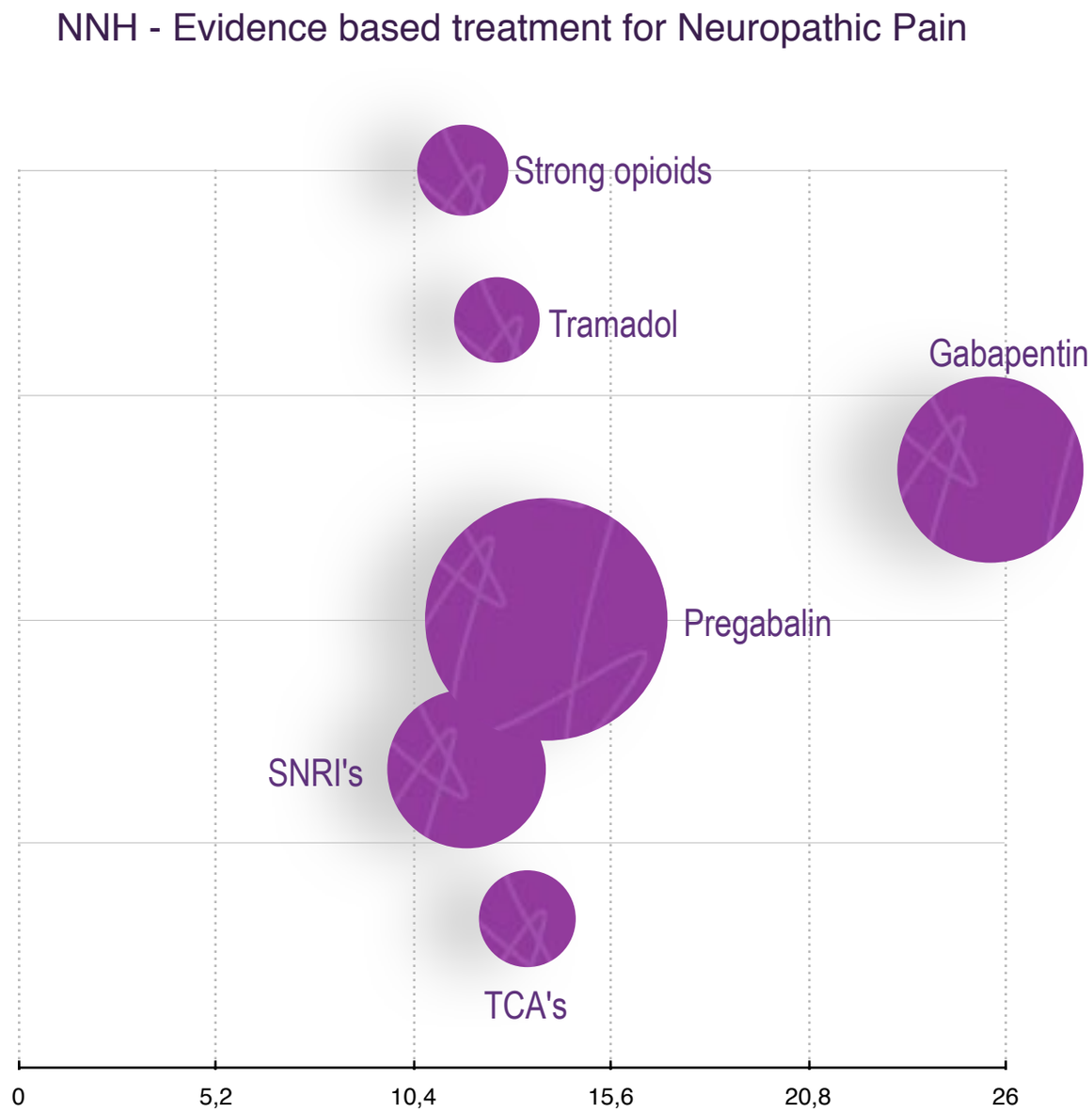


Main drugs for NeP and evidence available



adapted from Finnerup et al., 2015

Main drugs for NeP and evidence available



adapted from Finnerup et al., 2015

Evidence-based Recommendations

First line
Pregabalin/Gabapentin TCA's SNRI's

Second line
Capsaicin 8% (Peripheral NeP) Lidocaine patch (Peripheral NeP) Tramadol

Third line
Strong opioids Botulinum toxin (Peripheral NeP)

adapted from Finnerup et al., 2015

Evidence-based Recommendations

First line

Pregabalin/Gabapentin
TCA's
SNRI's

Second line

Capsaicin 8% (Peripheral NeP)
Lidocaine patch (Peripheral NeP)
Tramadol

Third line

Strong opioids
Botulinum toxin (Peripheral NeP)

Special situations

CENTRAL POST-STROKE PAIN
- TCA's, duloxetine, lamotrigine

SPINAL CORD INJURY
- TCA's, lamotrigine,

HIV ASSOCIATED POLYNEUROPATHY
-lamotrigine, cannabis

TRIGEMINAL NEURALGIA
carbamazepine, baclophen

Other drugs…

Inconclusive evidence or recommendation.

??

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lamotrigine
- Lacosamide
- NMDA antagonists
- tapentadol
- SSRI's
- Topiramate
- Zonisamide

Weak recommendation AGAINST use

- Cannabinoids
- Valproate

Strong recommendation AGAINST use

- Levetiracetam
- Mexiletine

adapted from Finnerup et al., 2015

Reasons why evidence based treatment seems so ineffective

1. Most studies were performed in patients with a single etiology of NeP (but with different mechanisms: eg, PHN);

2. In many studies: fixed dose regimen for each arm of the study;

3. High placebo effect;

4. Several drugs have not been included in larger trials (methadone, chlorpromazine, other topic agents)

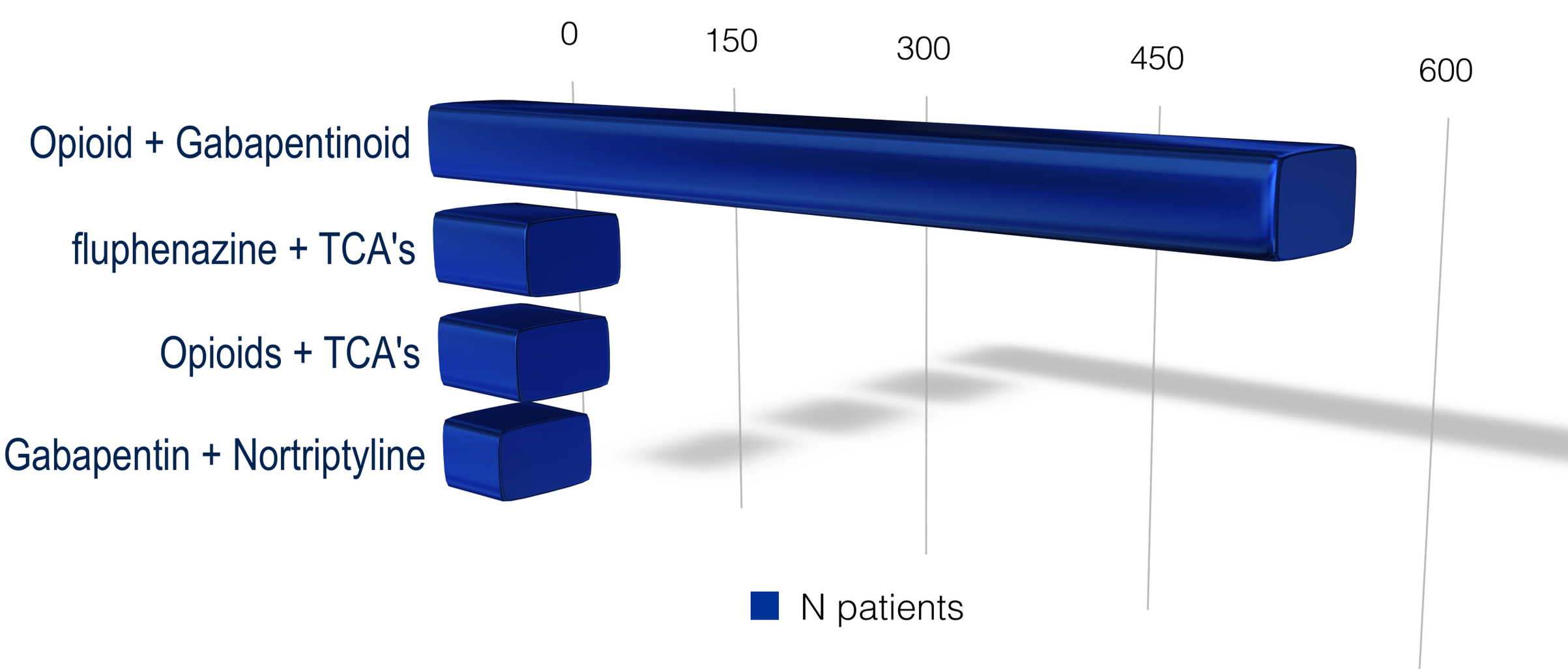
5. Most studies (>90%) assessed the effect of a single drug;

Can we do any better?

Combination therapy

1. At least half of chronic pain patients receive two or more drugs
2. Drug combination for Neuropathic pain [Chaparro et al,., 2012; Gilron 2013]

Main combinations [total of 21 RCT trials]



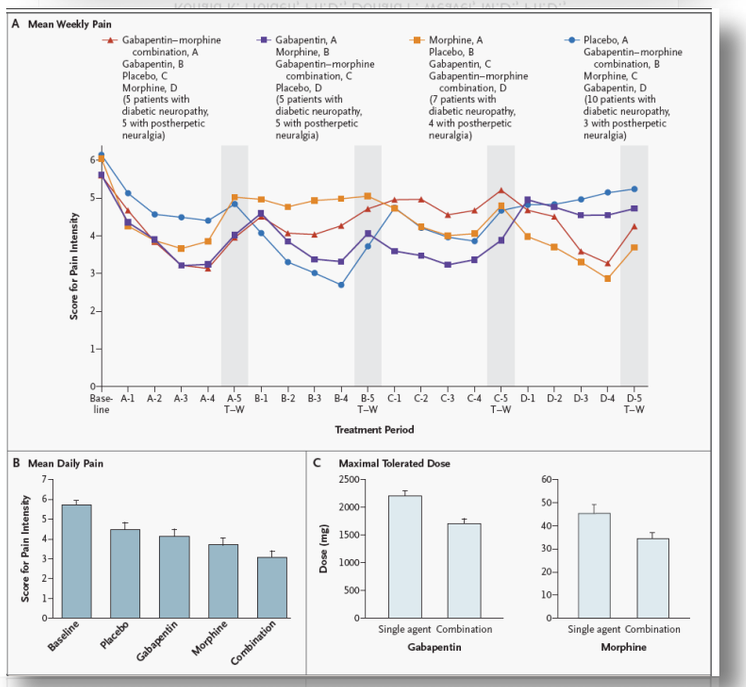
Combination therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

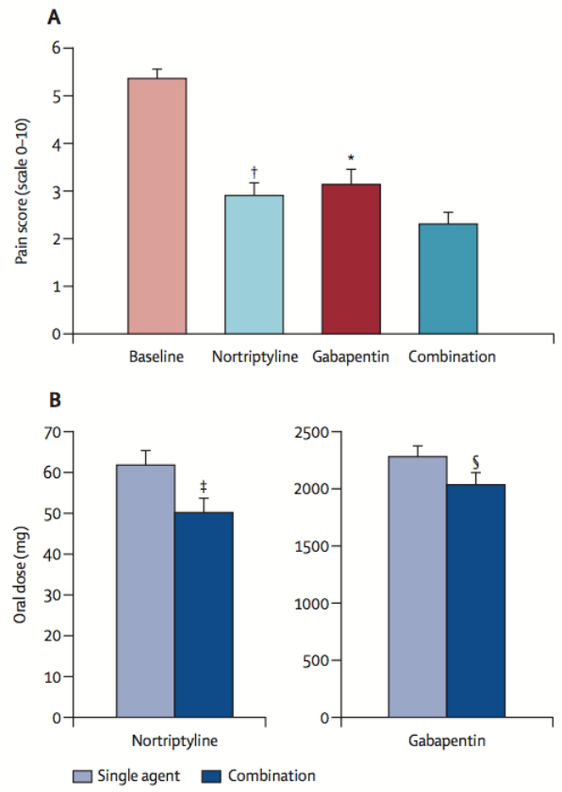
Morphine, Gabapentin, or Their Combination for Neuropathic Pain

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

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]

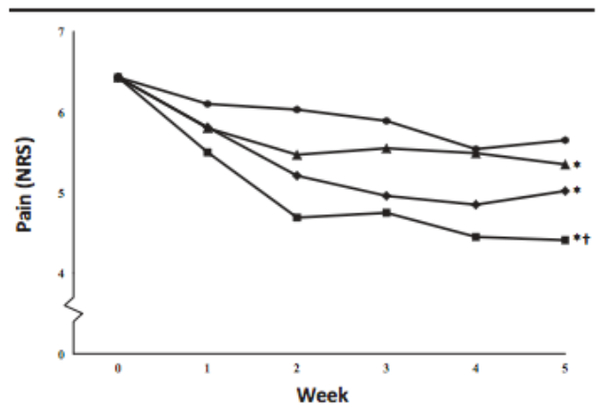


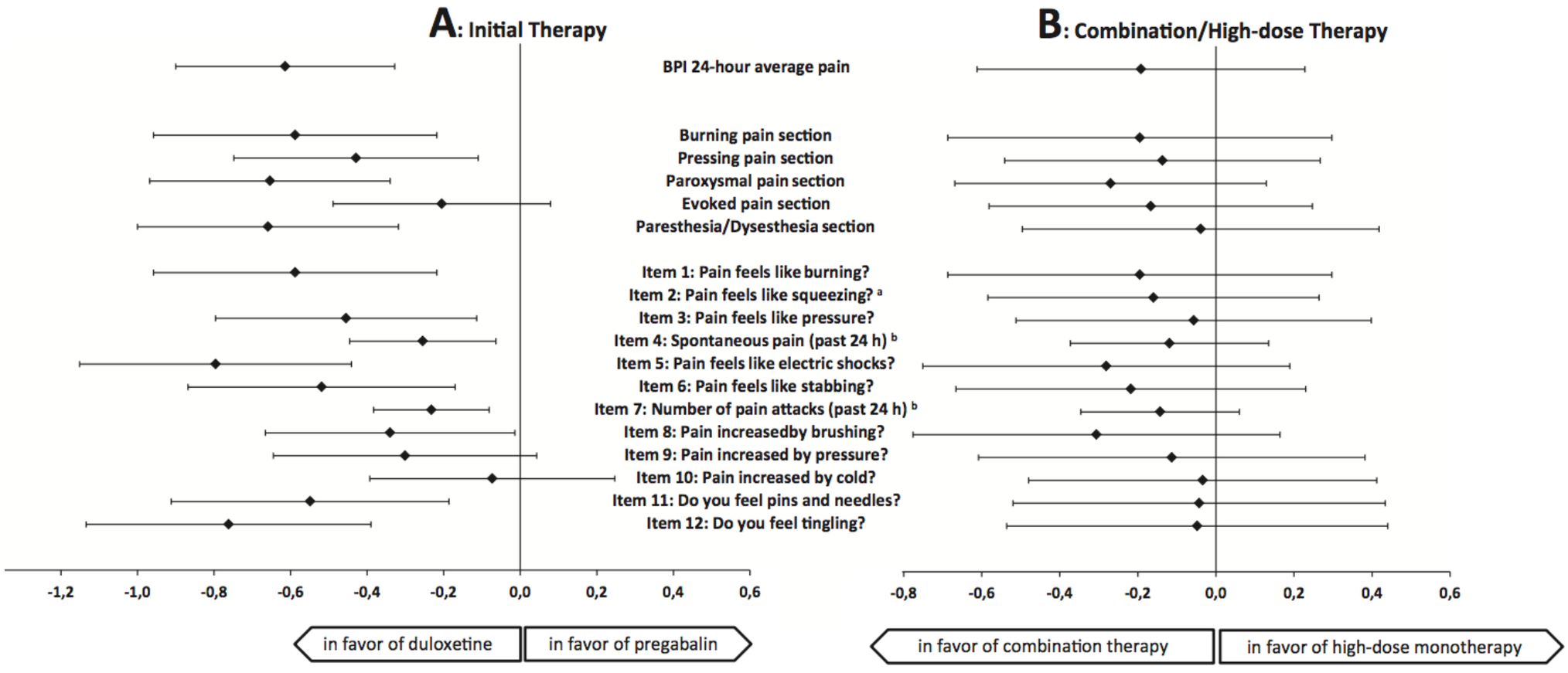
Figure 2. Change in total pain scores from baseline (0) to week 5 for the 4 different treatments. Placebo (●), pregabalin (▲), imipramine (♦) and combination (■). *Significantly different from placebo. †Significantly different from each monotherapy.

Combination therapy

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]

D. Bouhassira et al. / PAIN® 155 (2014) 2171–2179



XXII World Congress of Neurology
Santiago - Chile 2015
Changing Neurology Worldwide
Santiago, Chile, October 31 - November 5, 2015
WCN 2015

Combination therapy

IASP
PAIN® 155 (2014) 2171–2179
PAIN®
www.elsevier.com/locate/pain

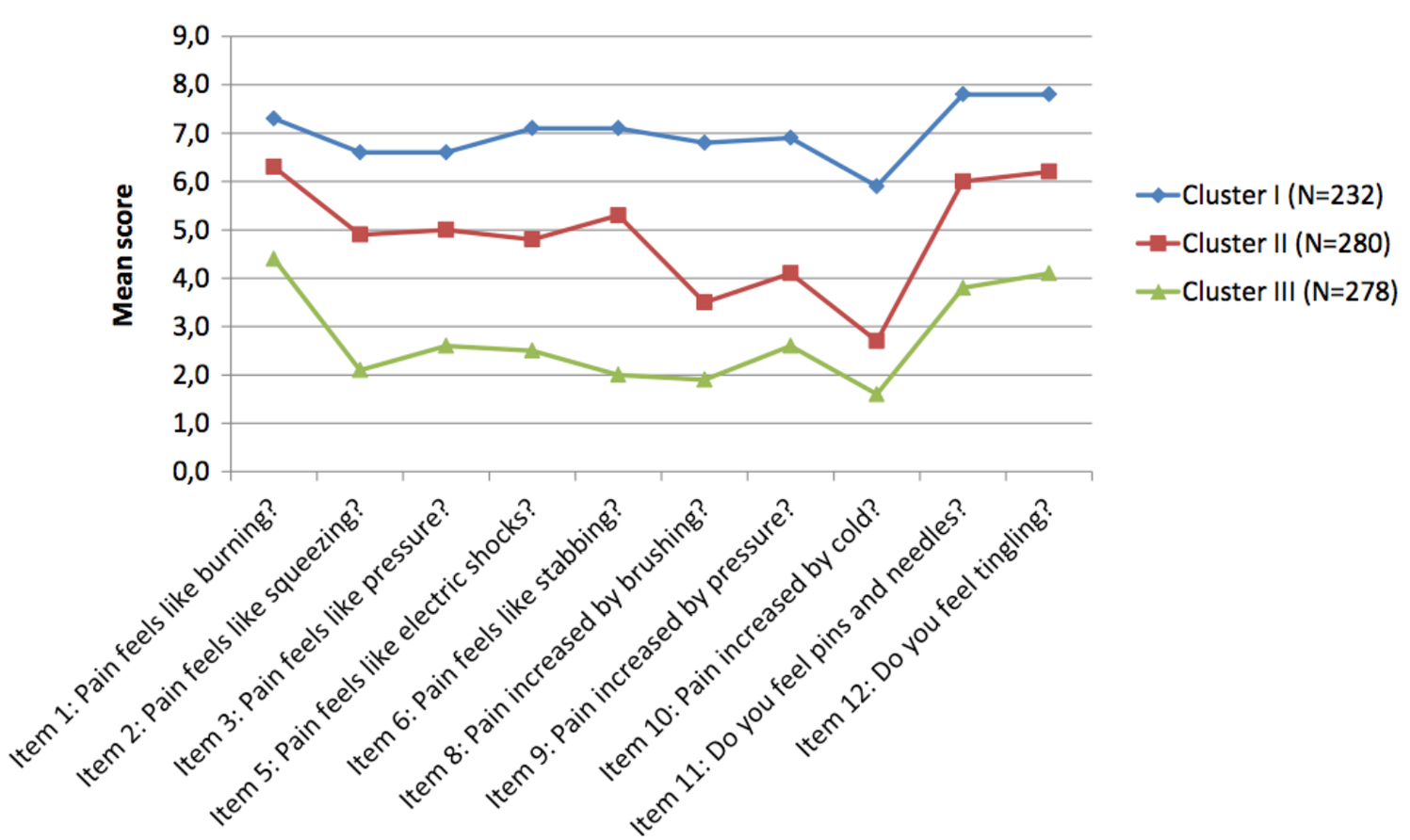
Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: Data from the randomized, double-blind, COMBO-DN study

Didier Bouhassira [a], Stefan Wilhelm [b,*], Alexander Schacht [c], Serge Perrot [d], Eva Kosek [e], Giorgio Cruccu [f], Rainer Freynhagen [g], Solomon Tesfaye [h], Alberto Lledó [i], Ernest Choy [j], Paolo Marchettini [k], Juan Antonio Micó [l], Michael Spaeth [m], Vladimir Skljarevski [n], Thomas Tölle [o]

..in patients not responding to initial 60 mg/d duloxetine, adding 300 mg/d pregabalin for combination treatment was particularly effective regarding the dimensions pressing pain and evoked pain,

…whereas maximizing the duloxetine dose to 120 mg/d appeared more beneficial regarding paresthesia/ dysesthesia.

3 clusters of symptoms



Mechanism- (symptom-) based approach to NeP

1. Response to neuropathic pain treatment does not correlate with specific etiologies of neuropathy;

2. Within a given etiology, multiple neuropathic pain symptoms (signs and symptoms) may coexist;

3. This may explain negative results in different drug trials where a single drug was used to control NeP of different symptoms (mechanisms) due to a single etiology *e.g: post-herpetic neuralgia, NeP due to painful diabetic polyneuropathy.*

Mechanism- (symptom-) based approach to NeP

1. Response to neuropathic pain treatment does not correlate with specific etiologies of neuropathy;

2. Within a given etiology, multiple neuropathic pain symptoms (signs and symptoms) may coexist;

3. This may explain negative results in different drug trials where a single drug was used to control NeP of different symptoms (mechanisms) due to a single etiology *e.g: post-herpetic neuralgia, NeP due to painful diabetic polyneuropathy.*

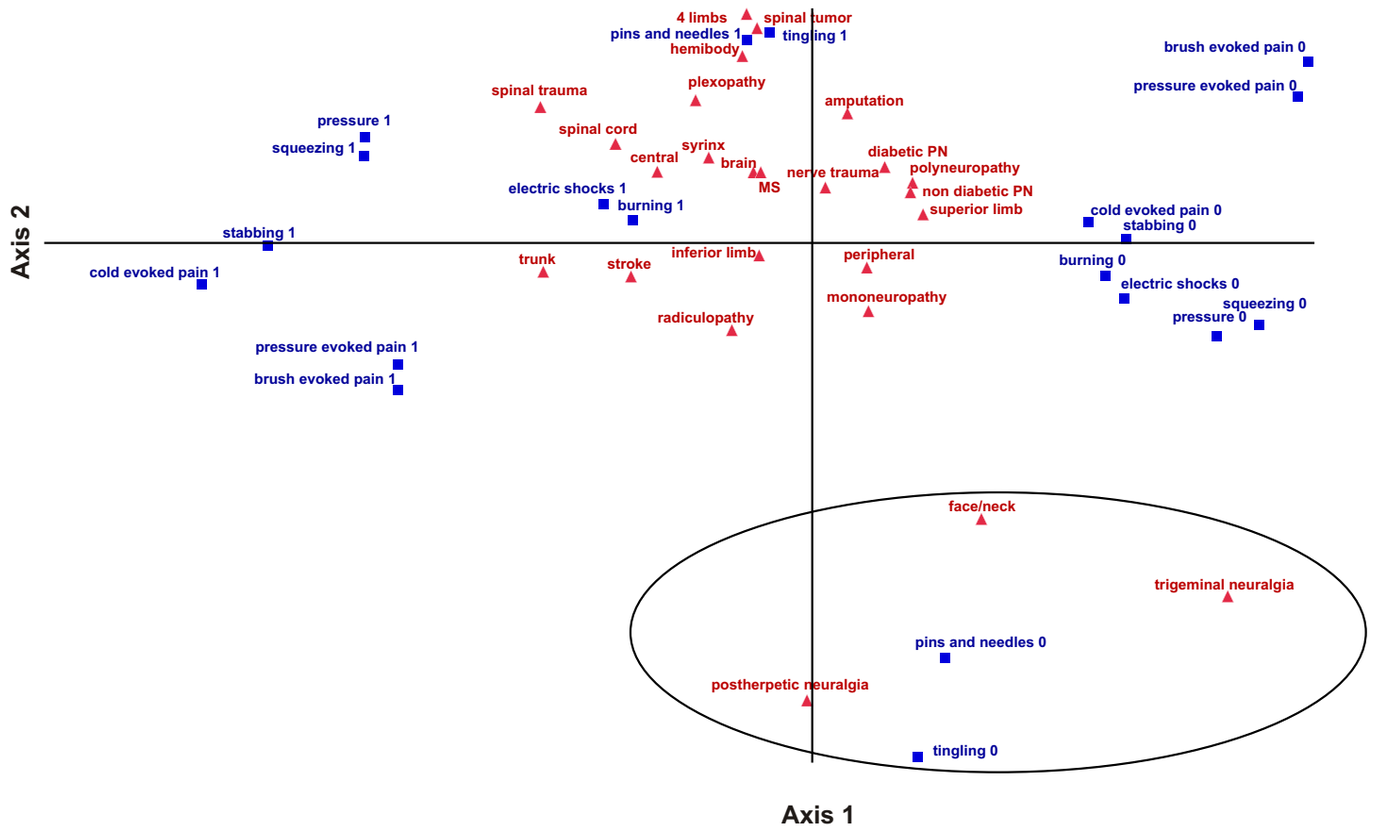
Pain 138 (2008) 343–353

PAIN

www.elsevier.com/locate/pain

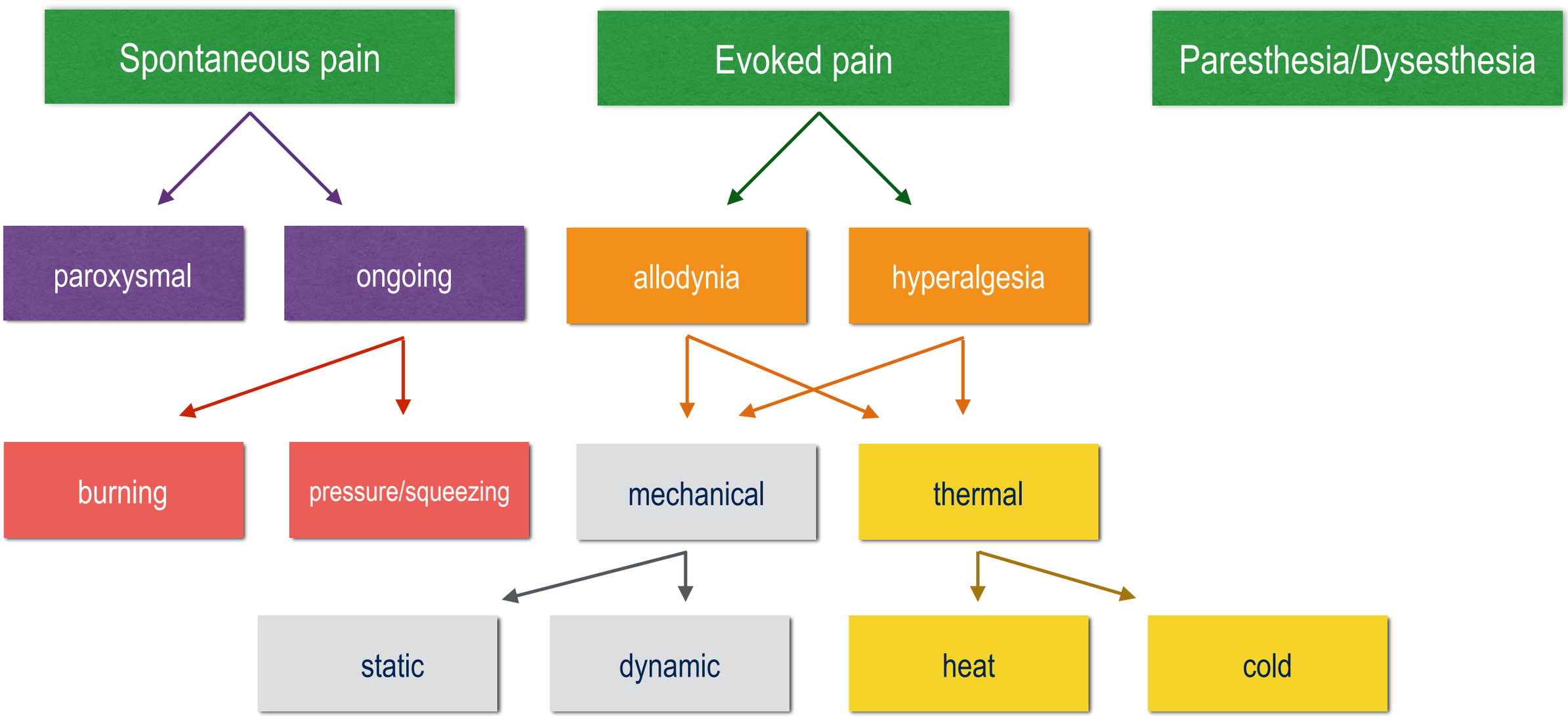
Neuropathic pain: Are there distinct subtypes depending on the aetiology or anatomical lesion?

N. Attal [a,b,*], C. Fermanian [c], J. Fermanian [d], M. Lanteri-Minet [e], H. Alchaar [c], D. Bouhassira [a,b]



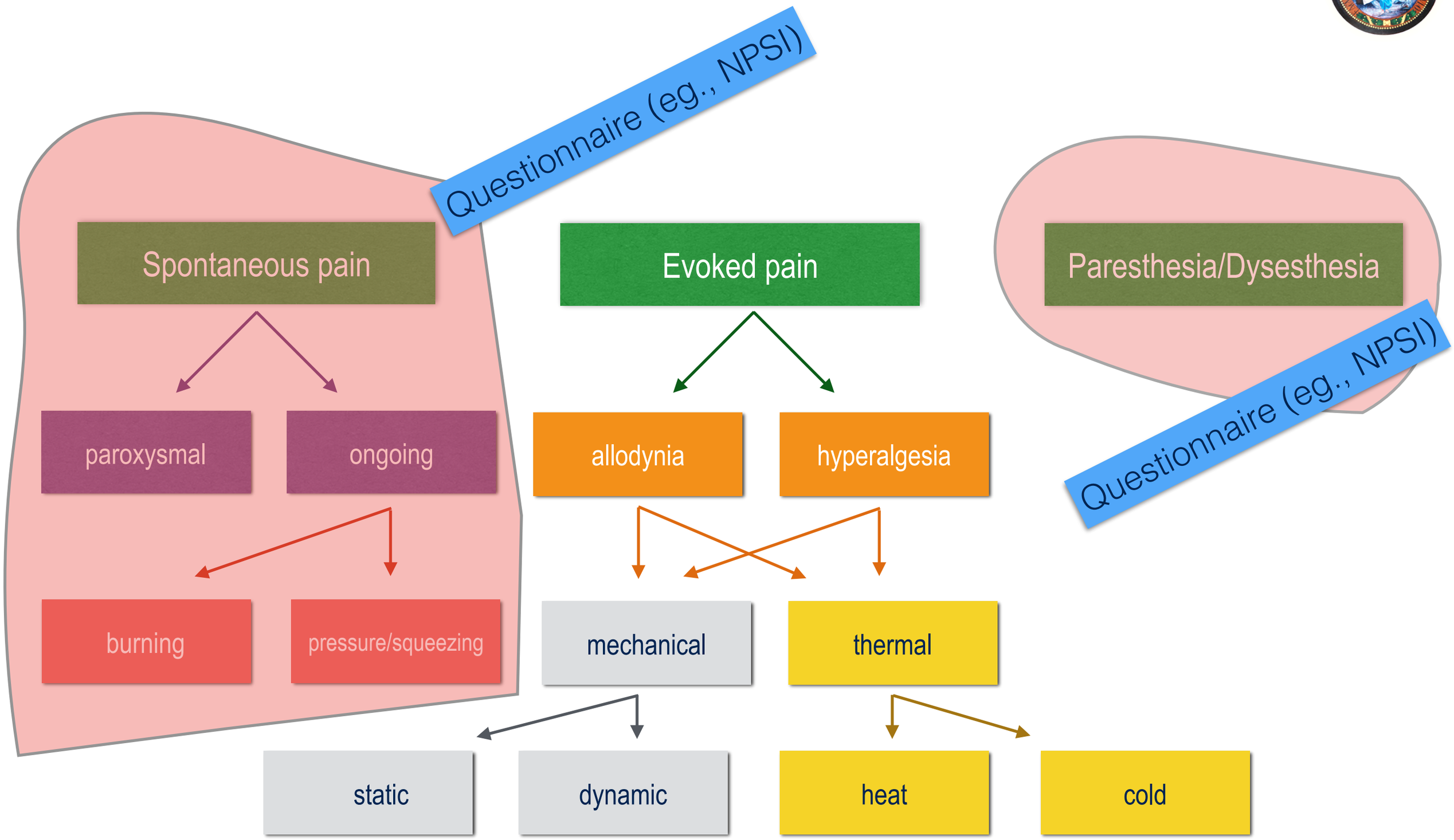
Mechanism- (symptom-) based approach to NeP

1. Different signs and symptoms in NeP

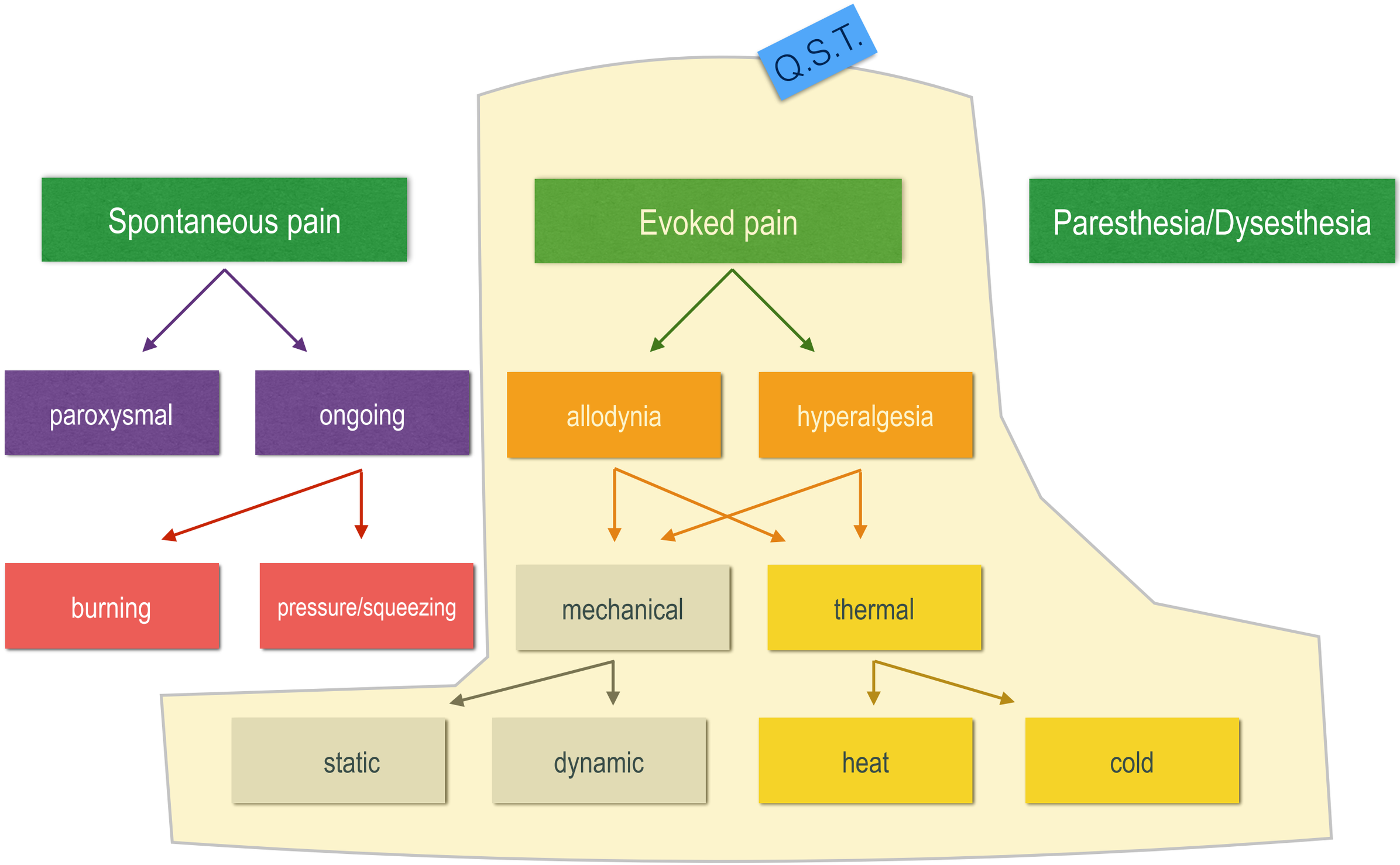


adapted from Bouhassira 2008

Mechanism- (symptom-) based approach to NeP



Mechanism- (symptom-) based approach to NeP

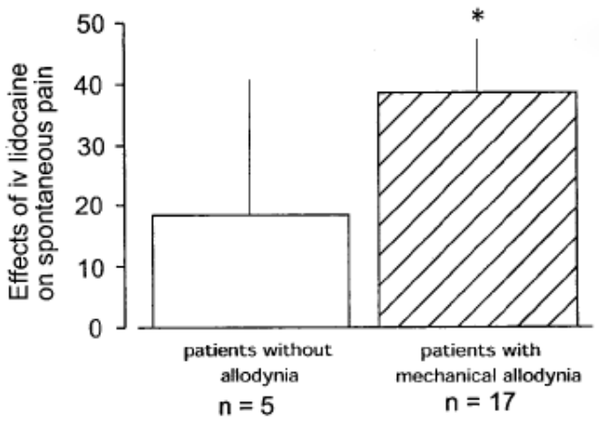


Mechanism- (symptom-) based approach to NeP

1. Data from post-hoc analyses: treatment response seem to depend on certain signs and symptoms and NOT on the etiology of NeP

Systemic lidocaine in pain due to peripheral nerve injury and predictors of response

N. Attal, MD, PhD; J. Rouaud, MD; L. Brasseur, MD; M. Chauvin, MD; and D. Bouhassira, MD, PhD



Pain 96 (2002) 375–383

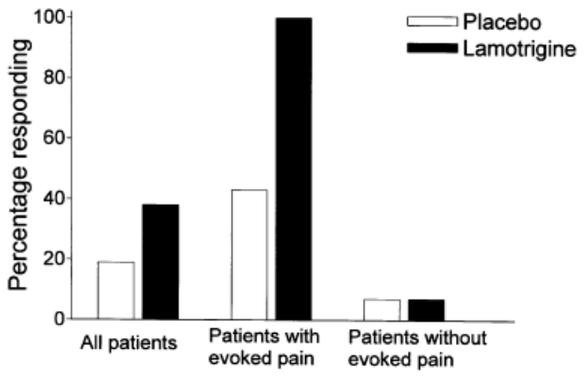
PAIN
www.elsevier.com/locate/pain

Lamotrigine in spinal cord injury pain: a randomized controlled trial

Nanna B. Finnerup[a,*], Søren H. Sindrup[b], Flemming W. Bach[a], Inger Lauge Johannesen[c], Troels S. Jensen[a]

[a]Department of Neurology and Danish Pain Research Center, Aarhus University Hospital, Århus, Denmark
[b]Department of Neurology, Odense University Hospital, Odense, Denmark
[c]Department of Rheumatology, Viborg Hospital, Viborg, Denmark

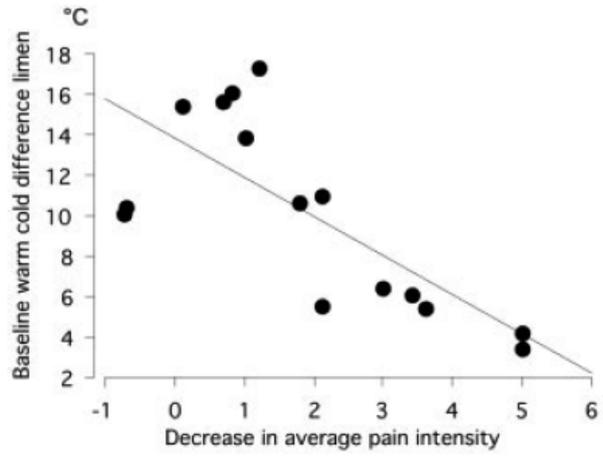
Received 24 August 2001; received in revised form 16 November 2001; accepted 29 November 2001



ORIGINAL ARTICLE

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

Danièle Ranoux, MD,[1] Nadine Attal, MD, PhD,[2–4] Francoise Morain, Clinical Research Assistant,[2–4] and D. Bouhassira[2–4]



Potential responders profiles :
patients with evoked pain (allodynia or hyperalgesia)

Preserved nociceptive function seems associated with better response to BTX-A

1. First PROSPECTIVE studies testing the mechanism based approach

IASP
PAIN® 153 (2012) 1815–1823
PAIN®
www.elsevier.com/locate/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 K. Schmidt [d], Karin L. Petersen [e,f], Michael C. Rowbotham [e,f], James N. Campbell [d]

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000000266

IASP
PAIN® xxx (2014) xxx–xxx
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,*]

Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype

A randomised, double-blind, and placebo-controlled phenotype panel study.

[1]Dyveke T. Demant, [2]Karen Lund, [2]Nanna B. Finnerup, [3]Jan Vollert, [3]Christoph Maier, [4,5]Märtha S. Segerdahl, [2]Troels S. Jensen, [1]Søren H. Sindrup

Responders profiles : patients with preserved nociceptive function

Higher effect in pain paroxysms and deep aching pain

Key messages

1. Pharmacological treatment has a main role in the treatment of NeP (but the analgesic effect of monotherapy is limited);

2. Antidepressants (TCA's, SSNRI's) and gabapentinoids are first line drugs in the treatment of NeP, followed by opioids and other drugs used for localized NeP such as botulinum toxin, lidocaine or high concentration capsaicin;

3. In general, drugs used for NeP as monotherapy have a relatively low efficacy (high NNT) and a large proportion of patients remain symptomatic despite its use. Also, trials on some specific NeP pain syndromes are scarce (eg., post-chemotherapy painful polyneuropathy) or have provided mainly negative results (eg., central post-stroke pain);

4. Combination therapy has been proposed to increase the analgesic effect of treatment with a lower side-effect profile by associating drugs with different mechanisms of action;

5. The rationale for a mechanism-based treatment of NeP has been put forward a few decades ago, and has been endorsed by *post-hoc* analyses of several trials and by recent studies.

References

1. Finnerup, Nanna B; Attal, Nadine; Haroutounian, Simon; McNicol, Ewan; Baron, Ralf; Dworkin, Robert H; Gilron, Ian; Haanpää, Maija; Hansson, Per; Jensen, Troels S; Kamerman, Peter R; Lund, Karen; Moore, Andrew; Raja, Srinivasa N; Rice, Andrew S C; Rowbotham, Michael; Sena, Emily; Siddall, Philip; Smith, Blair H; Wallace, Mark. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurology, Vol. 14, No. 2, 2015, p. 162-173.

2. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. Lancet Neurol. 2013 Nov;12(11):1084-95. Attal N, Bouhassira D, Baron R, Dostrovsky J, Dworkin RH, Finnerup N, Gourlay G, Haanpaa M, Raja S, Rice AS, Simpson D, Treede RD. Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? Eur J Pain. 2011 May;15(5):441-3.

3. Bouhassira D, Attal N. Diagnosis and assessment of neuropathic pain: the saga of clinical tools. Pain. 2011 Mar;152(3 Suppl):S74-83.

4. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ,Rice AS, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011 Jan;152(1):14-27.

5. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17(9):1113-e88.

Acknowledgements

Staff from the Pain Center,
Department of Neurology
University of São Paulo, Brazil

Manoel J Teixeira
Dra Lin T Yeng
Ricardo Galhardoni
Rubens G. Cury
Irina Raicher
Fernanda Valério
Luiz Henrique Dourado
Egberto Reis Barbosa
Victor Barboza
Irina Raicher
José Tadeu Siqueira
Silvia R D T de Siqueira
Patrick Stump
Erich Fonoff
Alexandra Zandonai
Luciana Bahia
Daniella Parravano
Paula B. Mileno
Natalia Scisci
Valquiria Silva
Antonia Rodrigues

France

Didier Bouhassira
Nadine Attal
Jean-Pascal Lefaucheur
Luis Garcia-Larrea