What you ought to know about neuropathic pain

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Definition of neuropathic pain

Old IASP definition: Neuropathic pain: ”Pain initiated or caused by a primary lesion or dysfunction in the nervous system”. (+neurogenic pain)

Merskey & Bogduk 1994

New suggested definition by NeuPSIG of IASP: Pain araising as a direct consequence of a lesion or disease affecting the somatosensory system

Treede et al. 2008

Current IASP definition: Pain caused by a lesion or disease of the somatosensory nervous system

Jensen et al. 2011

Conditions in which neuropathic pain may appear

Peripheral

Polyneuropathy
Mononeuropathy/mononeuropathy multiplex
Plexopathy
Radiculopathy

Causes: E.g., trauma, metabolic, pressure, cancer, infection, vitamin deficiences, autoimmune diseases, kidney disease, hereditary, radiation, medications, etc

Neuropathic pain conditions

Peripheral

Amputation: stump and phantom pain
Post herpetic neuralgia
CRPS type 2
Trigeminal and glossopharyngeal neuralgia

CNS conditions in which neuropathic pain may appear

- Stroke
- MS
- SCI including cordotomy
- Syringomyelia/bulbia
- Vascular malformation of brain or spinal cord
- Inflammatory disease other than MS
- Traumatic brain injury
- Tumor

Conditions in which neuropathic pain may appear

Peripheral

Polyneuropathy
Mononeuropathy/mononeuropathy multiplex
Plexopathy
Radiculopathy

Neuropathic pain conditions

Peripheral

Amputation: stump and phantom pain
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Lesion or disease of the somatosensory system usually is a painless condition!

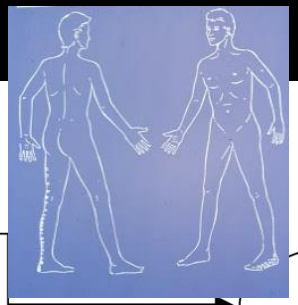
pain

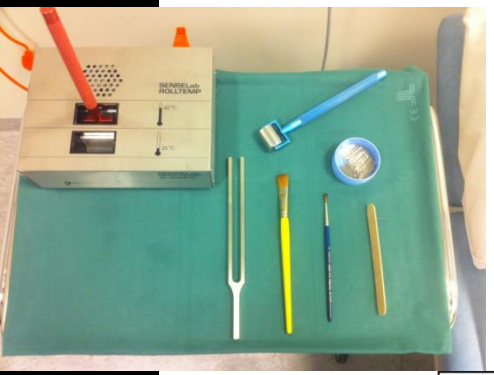
- MS
- SCI including cordotomy
- Syringomyelia/bulbia

brain or spinal cord

- Inflammatory disease other than MS
- Traumatic brain injury
- Tumor
- Abscess

NeP identification work-up algorithm for clinical and research use. 4 cornerstones and 3 levels of identification certainty





Leading complaint

Pain

History

Pain distribution neuroanatomically plausible and History suggests relevant lesion or disease

Unlikely to be neuropathic pain

Yes

Working hypothesis: Possible neuropathic pain

Examination

Confirmatory tests:

a: Negative or positive sensory signs, confined to innervation territory of the lesioned nervous structure

b: Diagnostic test confirming lesion or disease explaining neuropathic pain

Neither

Unconfirmed as neuropathic pain

Both

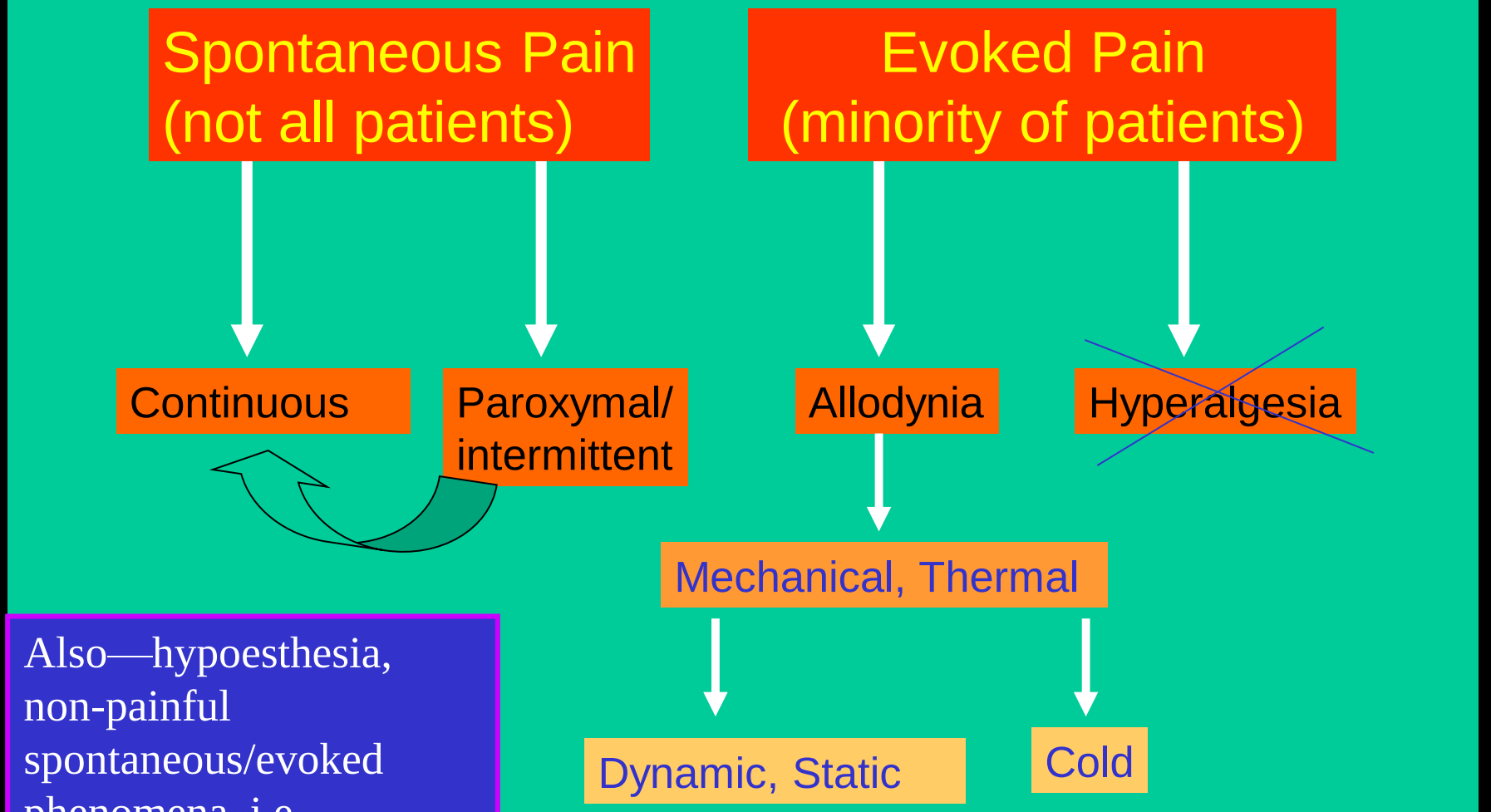
One

Definite neuropathic pain

Probable neuropathic pain

Treede et al. Neurology, 2008

Other clinical phenomenology not included in algorithm



Also—hypoesthesia, non-painful spontaneous/evoked phenomena, i.e., paresthesia, dysesthesia.

Any combinations=numerous phenotypes…..

Table 2
Aetiology of pain in the two groups of patients

Aetiology of neuropathic pain (n=89)	*n (%)*
Nerve trauma	44 (49.5)
Postherpetic neuralgia	12 (13.5)
Polyneuropathies	12 (13.5)
Begnin tumor	1 (1.1)
Spinal cord injury	5 (5.6)
Post-stroke pain	11 (12.4)
Multiple sclerosis	4 (4.5)
Aetiology of non-neuropathic pain (n=71)	
Osteoarthritis	40 (56.3)
Inflammatory arthropathies	23 (32.4)
Mechanical low back pain	8 (11.3)

No pathognomonic descriptor!

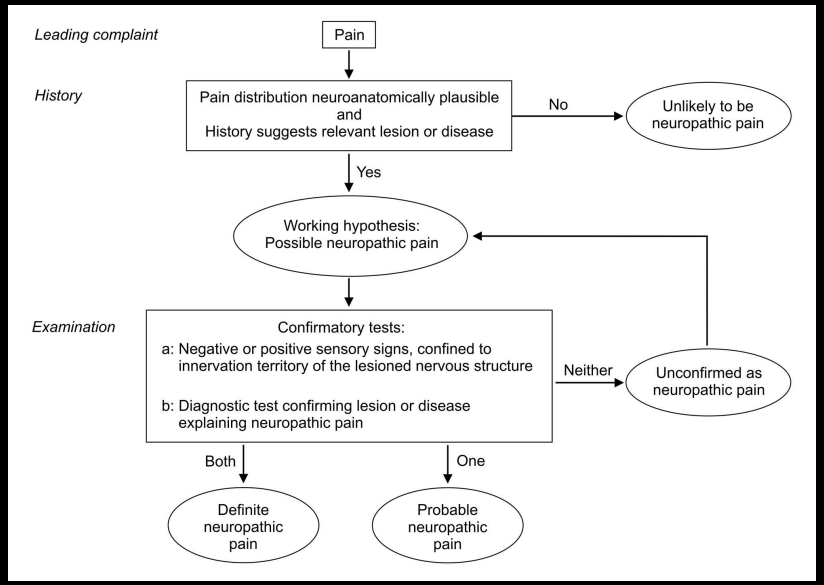
	Non-neuropathic pain *n* (%)	Neuropathic pain *n* (%)	Total *n* (%)	*P* value
Burning	21 (30.4)	56 (68.3)	77 (51.0)	<0.001
Squeezing	26 (37.7)	40 (48.8)	66 (43.7)	0.171
Painful cold	7 (10.1)	21 (25.6)	28 (18.5)	0.015
Electric shocks	12 (17.4)	53 (64.6)	65 (43)	<0.001
Lancinating	45 (65.2)	62 (75.6)	107 (70.9)	0.162
Tingling	11 (15.9)	49 (59.8)	60 (39.7)	<0.001
Pins and needles	12 (17.4)	54 (65.9)	66 (43.7)	<0.001
Itching	4 (5.8)	24 (29.3)	28 (18.5)	<0.001
Numbness	21 (30.4)	54 (65.9)	75 (49.7)	<0.001

Bouhassira et al. 2005

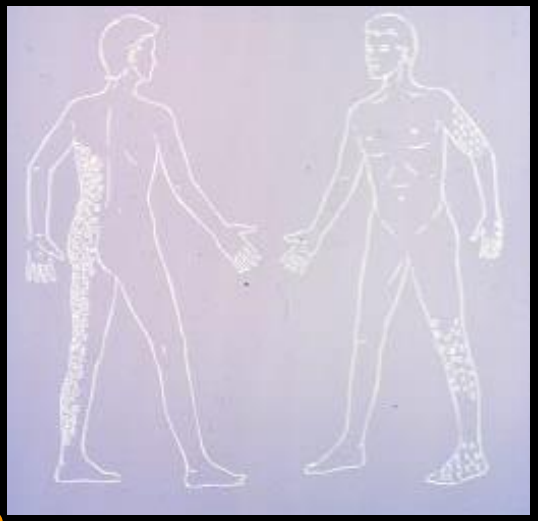
Definite neuropathic pain?

Pain in partial innervation territory of injured structure.

-Verified S1 radiculopathy, sensory abnormalities within S1 with continuous pain in heel only.
Aggravated by walking and pressure to heel area.
NeP? Nociceptive/inflammatory?

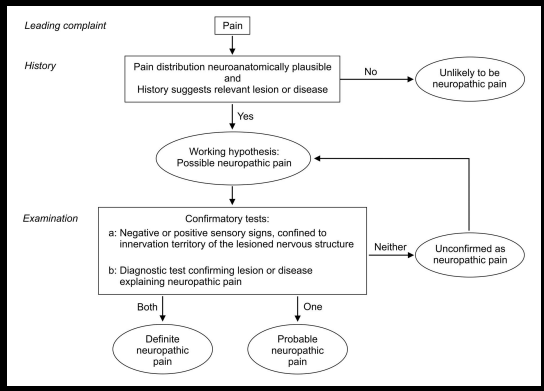


Definite neuropathic pain?

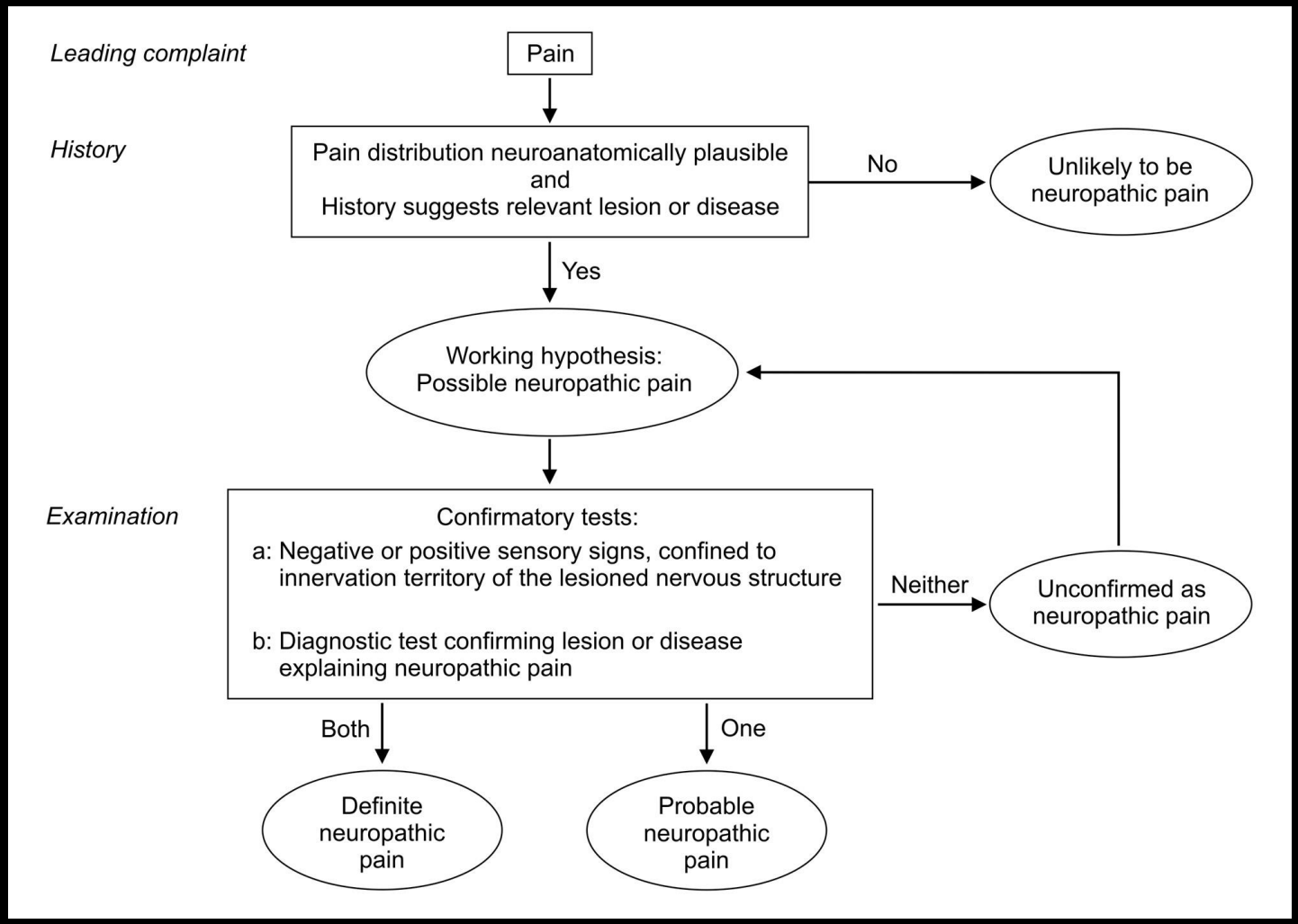


- Pain in stroke, SCI and MS with sensory abnormalities in painful area:
  - When, e.g., hemi or all-below - CNeP
  - When patchy - CNeP or m-s pain?

m-s = musculoskeletal



Identification work-up algorithm needs refinement.



Any help from questionnaires?

First Author, Year	Screening tool	Sample size	Sensitivity compared to clinical diagnosis	Specificity compared to clinical diagnosis	Predictive accuracy
Bennett, 2001	LANSS	N=60 (development) N=40 (validation)	85%	80%	Positive predictive value 86% Negative predictive value 84%
Bennett, 2005	S-LANSS	N=200 (validation)	74%	76% (unaided completion) 83% (aided completion)	Not reported
Krause and Backonja, 2008	NPQ	N=382 (development and validation)	66%	74%	71%
Bouhassira, 2006	DN4	N=160 (development and validation)	83%	90%	86%
Freynhagen, 2006	painDETECT	N=392 (validation)	85%	80%	83%
Portenoy, 2006	ID-Pain	N=586 (development) N=308 (validation)	Not reported	Not reported	Not reported

Abbreviations:
LANSS = Leeds Assessment of Neuropathic Symptoms and Signs
S-LANSS = Self-complete Leeds Assessment of Neuropathic Symptoms and Signs
NPQ = Neuropathic Pain Questionnaire
DN4 = Douleur neuropathique en 4 questions

Miss out on up to 20%

Haanpää et al. 2011

DN4

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**		

Bouhassira et al. 2005

S-LANSS

1. **In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?**
   - a) NO – I don't get these sensations (0)
   - b) YES – I get these sensations often (5)

2. **Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?**
   - a) NO – The pain does not affect the colour of my skin (0)
   - b) YES – I have noticed that the pain does make my skin look different from normal (5)

3. **Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.**
   - a) NO – The pain does not make my skin in that area abnormally sensitive to touch (0)
   - b) YES – My skin in that area is particularly sensitive to touch (3)

4. **Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.**
   - a) NO – My pain doesn't really feel like this (0)
   - b) YES – I get these sensations often (2)

5. **In the area where you have pain, does your skin feel unusually hot like a burning pain?**
   - a) NO – I don't have burning pain (0)
   - b) YES – I get burning pain often (1)

6. **Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?**
   - a) The painful area feels no different from the non-painful area (0)
   - b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area (5)

7. **Gently press on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?**
   - a) The painful area does not feel different from the non-painful area (0)
   - b) I feel numbness or tenderness in the painful area that is different from the non-painful area (3)

Scoring: a score of 12 or more suggests pain of predominantly neuropathic origin

Bennett et al. 2005

Table 1. *painDETECT questionnaire*

Item	Score
*Gradation of pain**	
• Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	0–5
• Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	0–5
• Is light touching (clothing, a blanket) in this area painful?	0–5
• Do you have sudden pain attacks in the area of your pain, like electric shocks?	0–5
• Is cold or heat (bath water) in this area occasionally painful?	0–5
• Do you suffer from a sensation of numbness in the areas that you marked?	0–5
• Does slight pressure in this area, e.g. with a finger, trigger pain?	0–5
Pain course pattern	
Please select the picture that best describes the course of your pain:	
 Persistent pain with slight fluctuations	0
 Persistent pain with pain attacks	–1
 Pain attacks without pain between them	+1
 Pain attacks with pain between them	+1
Radiating pain	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5
Questions used to document pain, but which were not used in the scoring, are not shown

>19 predom. neuropathic type of pain, <12 nocic. type of pain

Freynhagen et al. 2006

Table 2 Summary statistics for participants classified according to the new IASP grading system. Data are presented as median and range

Characteristics	Classification Based on the IASP Grading System: Does not Fulfill Criteria 1 + 2 (N = 90)	Fulfill Criteria 1 + 2 (not 3 or 4) (N = 8)	Fulfill Criteria 1 + 2 + (3 and/or 4) (N = 22)	*P* value (Independent sample Mann–Whitney *U*-Test)
Age	47 (23–87)	45 (33–74)	45 (30–73)	0.748
Body mass index	26.33 (15.94–39.61)	25.34 (22.32–36.75)	26.52 (17.99–35.41)	0.933
Pain duration (months)	72 (6–360)	36 (24–384)	120 (24–396)	0.251
Average pain intensity over past week	7 (3–10)	6 (4–9)	7 (3–9)	0.351
Worst pain intensity over past week	9 (5–10)	8 (5–10)	9 (5–10)	0.259

N=120

Vaegter et al. 2013

Table 3 Summary statistics for participants classified according to their score on the PainDETECT Questionnaire. Data are presented as median and range

Characteristics	Classification Based on PainDETECT Score: PDQ: 0–13 (N = 13) Unlikely Neuropathic	PDQ: 13–18 (N = 52) Unclear	PDQ: 19–38 (N = 55) Likely Neuropathic Pain	*P* Value (Independent Sample Mann–Whitney *U*-Test)
Age	48 (33–79)	45 (23–87)	47 (24–84)	0.178
Body mass index	23.39 (15.94–35.41)	25.11 (17.31–36.75)	27.47 (17.99–39.61)	0.1
Pain duration (months)	72 (12–384)	72 (12–396)	72 (6–300)	0.956
Average pain intensity over past week	7 (5–8)	7 (3–10)	7 (3–10)	0.234
Worst pain intensity over past week	8 (5–10)	9 (5–10)	9 (5–10)	0.178

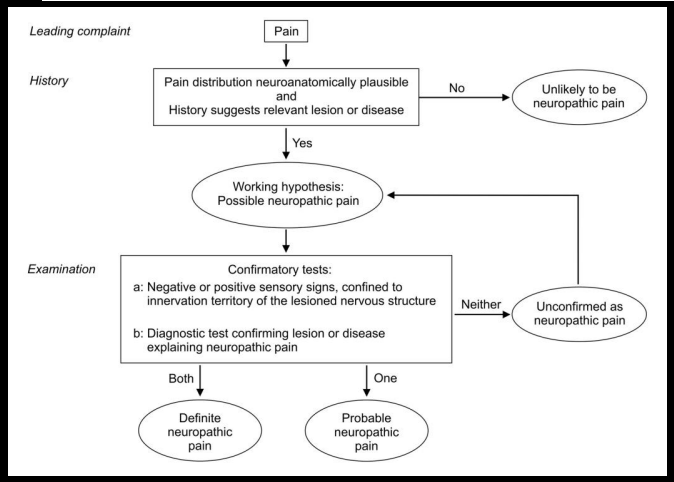


Table 1. painDETECT questionnaire

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Pain course pattern	
Please select the picture that best describes the course of your pain:	
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Radiating pain	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5
Questions used to document pain, but which were not used in the scoring, are not shown

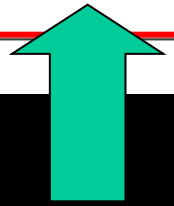
Epidemiology of neuropathic pain based on questionnaires is a mess!

Prevalence of 3-18 % !!

Table 6 Comparison of currently published studies examining prevalence of chronic pain with neuropathic features

Citation	Subjects Studied	Methodology	Outcome Measures	Results—Chronic Pain with Neuropathic Features	Greatest Limitations in Generalization of Results
Bouhassira et al. [15]	23,712 subjects	Mailed questionnaires	Chronic pain prevalence, DN4	6.9% prevalence	Lack of pain syndrome identification, Pre-determined survey audience
Dieleman et al. [35]	1,116,215 person years	General patient database assessment	Incidence of new cases of NeP	0.82% yearly incidence of new cases of NeP	Retrospective database search, no identification of subjects outside of medical system, no formal definition of NeP
Gustorff et al. [14]	7,707 subjects	Internet inquiry survey	LANSS and characteristic NeP items	3.3% prevalence	Pre-determined pool of registered subjects, potential technological limitations, screening for only major etiologies of NeP
Torrance et al. [5]	6,000 subjects	Mailed questionnaires to patients in family practices	LANSS	8.2% prevalence	No identification of subjects outside of medical system
Toth et al. (current study)	1,207 subjects	Randomized telephone survey	Chronic pain prevalence, DN4	17.9% prevalence	Lack of pain syndrome identification, potential identification of pain syndromes unlikely to be NeP

Direct comparisons of these studies are limited by methodological differences as outlined.
NeP = neuropathic pain; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs.



Toth et al. 2009

Some aired issues with DN4, LANSS and PainDetect

- Descriptors not specific
- Descriptors need to be explained-not self-explanatory, e.g., allodynia
- Must be restricted to body areas when applied
- Etiology specific descriptors? DN4 not for cancer related NeP? PD not for trigeminal? Validation needed for each NeP etiology
- PainDetect and algorithm don’t fit.
- LANSS more “open” than DN4
- Validation of DN4 with nociceptive pains that may have NeP components
- Mixed pain not in original DN4 and LANSS studies
- Linguistic and cultural differences

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 SC Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace

NeuPSIG/IASP

Lancet Neurology, online 2015

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls;[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34] ‡The long-term safety of repeated applications of high-concentration capsaicin patches in patients has not been clearly established, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. §Sustained release oxycodone and morphine have been the most studied opioids (maximum doses of 120 mg/day and 240 mg/day, respectively, in clinical trials; appendix); long-term opioid use might be associated with abuse, particularly at high doses, cognitive impairment, and endocrine and immunological changes.[35-37]

Table 2: **Drugs or drug classes with strong or weak recommendations for use based on the GRADE classification**

Not Trigeminal neuralgia

Finnerup et al., online 2015

	Comparisons*	Participants†	Active pain relief	Placebo	Number needed to treat (95% CI)	Susceptibility to bias‡
Tricyclic antidepressants	15	948	217/473	85/475	3·6 (3·0–4·4)	1973
Serotonin-noradrenaline reuptake inhibitors	10	2541	676/1559	278/982	6·4 (5·2–8·4)	1826
Pregabalin	25	5940	1359/3530	578/2410	7·7 (6·5–9·4)	2534
Gabapentin§	14	3503	719/2073	291/1430	7·2 (5·9–9·1)	1879
Tramadol	6	741	176/380	96/361	4·7 (3·6–6·7)	982
Strong opioids	7	838	211/426	108/412	4·3 (3·4–5·8)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10·6 (7·4–18·8)	70¶
Botulinum toxin A	4	137	42/70	4/67	1·9 (1·5–2·4)	678

Finnerup et al., online 2015

Panel: Drugs or drug classes with inconclusive recommendations for use or recommendations against use based on the GRADE classification

Inconclusive recommendations

- Combination therapy
- Capsaicin cream
- Carbamazepine
- Clonidine topical
- Lacosamide
- Lamotrigine
- NMDA antagonists
- Oxcarbazepine
- SSRI antidepressants
- Tapentadol
- Topiramate
- Zonisamide

Weak recommendations against use

- Cannabinoids
- Valproate

Strong recommendations against use

- Levetiracetam
- Mexiletine

Finnerup et al., online 2015

	First-line drugs			Second-line drugs			Third-line drugs	
	Serotonin-noradrenaline reuptake inhibitors duloxetine and venlafaxine	Tricyclic antidepressants	Pregabalin, gabapentin, gabapentin extended release or enacarbil	Tramadol	Capsaicin 8% patches	Lidocaine patches	Strong opioids	Botulinum toxin A
Quality of evidence	High	Moderate	High	Moderate	High	Low	Moderate	Moderate
Balance between desirable and undesirable effects								
Effect size	Moderate	Moderate	Moderate	Moderate	Low	Unknown	Moderate	Moderate
Tolerability and safety*	Moderate	Low-moderate	Moderate-high	Low-moderate	Moderate-high	High	Low-moderate	High
Values and preferences	Low-moderate	Low-moderate	Low-moderate	Low-moderate	High	High	Low-moderate	High
Cost and resource allocation	Low-moderate	Low	Low-moderate	Low	Moderate-high	Moderate-high	Low-moderate	Moderate-high
Strength of recommendation	Strong	Strong	Strong	Weak	Weak	Weak	Weak	Weak
Neuropathic pain conditions	All	All	All	All	Peripheral	Peripheral	All	Peripheral

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Common side-effects: antidepressants: somnolence, constipation, dry mouth (particularly with tricyclic antidepressants), and nausea (particularly duloxetine); pregabalin or gabapentin: somnolence, dizziness, and weight gain; opioids (including tramadol): constipation, nausea, vomiting, tiredness, somnolence, dizziness, dry mouth, and itch; lidocaine patches: local irritation; capsaicin patches: local pain, oedema, and erythema; botulinum toxin A: local pain; see the appendix for further information about safety issues.

Table 3: Summary of GRADE recommendations

Finnerup et al., online 2015

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine Gabapentin-morphine TCA Gabapentin Nicotine agonist** Nitrate derivatives** Oxycodone Pregabalin TCA[b] Tramadol alone or with acetaminophen Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin/venlafaxine* Levodopa*	Carbamazepine Phenytoin	Capsaicin cream Lacosamide Lamotrigine Memantine Mexiletine Mianserin NK1 antagonist** Oxcarbazepine SSRI Topical clonidine Topiramate Valproate Zonisamide	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol[c]
PHN	Capsaicin 8% patch** Gabapentin Gabapentin ER** Lidocaine plasters Opioids (morphine, oxycodone, methadone) Pregabalin TCA[b]	Capsaicin cream Valproate*		Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids
Classical trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Baclofen* Lamotrigine* Pimozide* Tizanidine*		Carbamazepine Oxcarbazepine	Surgery
Central pain[e]	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids		Carbamazepine Gabapentin Lamotrigine (SCI) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

Attal et al. 2010

What's going on?

A few among many unsolved issues……..

NeP is a clinical description and not a diagnosis!

EJP
European Journal of Pain

POSITION PAPER

2013

Neuropathic pain needs systematic classification

N.B. Finnerup[1], J. Scholz[2], N. Attal[3], R. Baron[4], M. Haanpää[5], P. Hansson[6], S.N. Raja[7], A.S.C. Rice[8], W. Rief[9], M.C. Rowbotham[10], D.M. Simpson[11], R.-D. Treede[12]

Table 1 ICD-10 codes related to neuropathic pain (bold font) and examples of disorders for which neuropathic pain is not specified.

Chapter	Disease/Symptom	ICD-10 code
Diseases of the nervous system	**Trigeminal neuralgia**	**G50.0**
	Disorders of cranial nerves	G51-G53
	Post-zoster neuralgia[a]	**G53.0**
	Nerve root and plexus disorders/compressions	G54-55
	Phantom limb syndrome with pain	**G54.6**
	Polyneuropathies	G60-64
Diseases of the circulatory system	Other specified peripheral vascular diseases	
	Erythromelalgia	**I73.8**
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	Hyperesthesia	R20.0
	Chronic intractable pain	R52.1
	Other chronic pain	R52.2
	Pain, unspecified	R52.9

ICD, International Classification of Diseases.
[a]Extracranial manifestations of post-zoster neuralgia are not classified.

-Not an unommon problem on a population basis
-Should be shown how it affects patient and society, suffering + costs (work place and health care)
-Underreporting of conditions where pain is the dominating symptom

NeuPSIG wants to:
-push for adding missing disorders (common and uncommon such as, e.g., PEPD, FEPS) and correct inaccurate designations into ICD 11 (e.g., IEM)

-to introduce a separate code for primary NePs and NePs that are manifests of other diseases

ICD 10

R520-akut smärta

R521-kronisk intraktabel smärta

R522- annan kronisk smärta

R529-uspecificerad smärta

Sverigespecial ICD 10—Sanktionerat av Socialstyrelsen

R522A-långvarig nociceptiv smärta

R522B-långvarig neuropatisk smärta

R522C-långvarig smärta utan känd orsak

Exempel: G629+R522B; G359+R522B; M541+R522B

PAIN

Pain 77 (1998) 227–229

Editorial

Towards a mechanism-based classification of pain?

Clifford J. Woolf*, Gary J. Bennett, Michael Doherty, Ronald Dubner, Bruce Kidd, Martin Koltzenburg, Richard Lipton, John D. Loeser, Richard Payne, Eric Torebjork

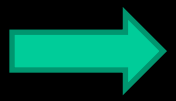
Categories of pain and possible mechanisms

Transient pain*
Nociceptor specialization

Tissue injury pain
Primary afferent
Sensitization
Recruitment of silent nociceptors
Alteration in phenotype
Hyperinnervation
CNS mediated
Central sensitization recruitment, summation, amplification

Nervous system injury pain
Primary afferent
Acquisition of spontaneous and stimulus-evoked activity by nociceptor axons and somata at loci other than peripheral terminals
Phenotype change
CNS mediated
Central sensitization
Deafferentation of 2nd order neurons
Disinhibition
Structural reorganization

*Transient pain refers to the response to a noxious stimulus which does not produce long term sequelae, e.g. a pin prick.



Mechanism-based treatment

Table 1. painDETECT questionnaire

Item	Score
*Gradation of pain**	
• Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?	0-5
• Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?	0-5
• Is light touching (clothing, a blanket) in this area painful?	0-5
• Do you have sudden pain attacks in the area of your pain, like electric shocks?	0-5
• Is cold or heat (bath water) in this area occasionally painful?	0-5
• Do you suffer from a sensation of numbness in the areas that you marked?	0-5
• Does slight pressure in this area, e.g. with a finger, trigger pain?	0-5
Pain course pattern	
Please select the picture that best describes the course of your pain:	
 Persistent pain with slight fluctuations	0
 Persistent pain with pain attacks	-1
 Pain attacks without pain between them	+1
 Pain attacks with pain between them	+1
Radiating pain	
Does your pain radiate to other regions of your body? Yes/No	+2/0

*For each question: never, 0; hardly noticed, 1; slightly, 2; moderately, 3; strongly, 4; very strongly, 5
Questions used to document pain, but which were not used in the scoring, are not shown

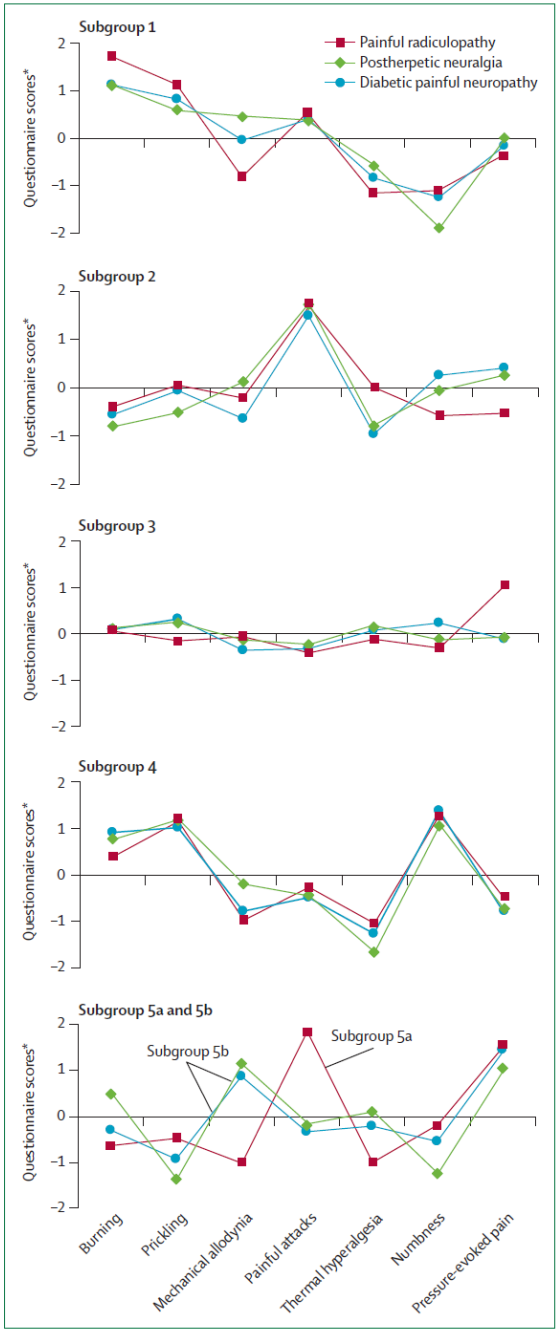


Figure: Subgroups of patients based on sensory symptoms assessed with PainDETECT

Baron et al. 2012

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,*]

IN=normal QST for warm and cold +hypersensitivity

PNP=38; PNI=38; PHN=7

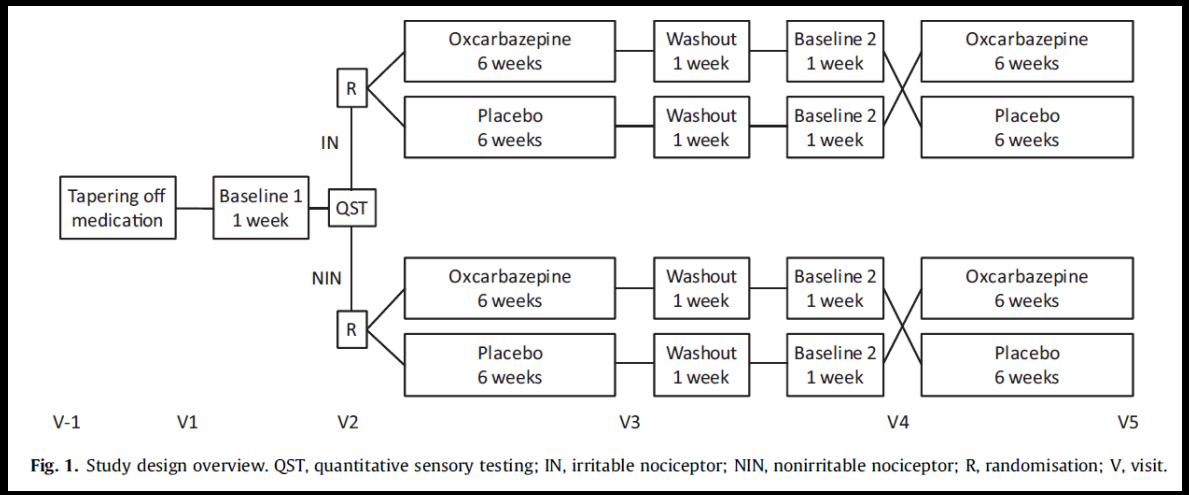


Fig. 1. Study design overview. QST, quantitative sensory testing; IN, irritable nociceptor; NIN, nonirritable nociceptor; R, randomisation; V, visit.

Patients included safety data analysis n=83 (IN: 31, NIN: 52)
Patients completing study **PP** n=39 (IN: 10, NIN: 29)
Patients included in **ITT** analysis n=83 (IN: 31, NIN: 52)
Patients with **LOCF** data n=70

Table 3

Numeric pain, pain-related sleep disturbance, and health related quality-of-life (QoL) ratings (NRS, 0–10) from 83 patients (intention-to-treat population) with peripheral neuropathic pain with either irritable nociceptor (IN, n = 31) or nonirritable nociceptor (NIN, n = 52) phenotype during treatment with oxcarbazepine and placebo.

	Oxcarbazepine NRS mean (SD)		Placebo NRS mean (SD)		Treatment effect NRS mean difference (95% CI)[b,c]		Interaction treatment and phenotype[d] NRS mean difference (95% CI)	
Pain category	Baseline	Change[a]	Baseline	Change[a]	Difference	*P*-value	Difference	*P*-value
Total								
IN	6.4 (1.5)	−1.4 (1.7)	6.1 (1.9)	−0.2 (1.6)				
NIN	6.1 (1.8)	−0.7 (1.6)	6.2 (1.7)	−0.1 (1.6)	−0.7 (−1.2 to −0.1)	0.015	−0.7 (−1.4 to −0.01)	0.047

Table 4

Numeric pain scale (NRS, 1-10) ratings from 83 patients (intention-to-treat population) with peripheral neuropathic pain analysed with thermal sensation, sensation gain, and the dimensions of neuropathic pain symptom inventory (NPSI)* as predictors of effect of oxcarbazepine.

Predictor	Oxcarbazepine NRS mean (SD)		Placebo NRS mean (SD)		Treatment[b] effect NRS mean difference (95% CI)		Interaction[c] treatment and phenotype NRS mean difference (95% CI)	
	Baseline	Change[a]	Baseline	Change[a]	Difference	*P*-value	Difference[d]	*P*-value[#]
Thermal sensation								
Preserved (n = 42)	6.2 (1.5)	−1.4 (1.7)	6.0 (1.8)	−0.3 (1.7)				
Abnormal (n = 41)	6.2 (1.8)	−0.6 (1.5)	6.3 (1.8)	+0.1 (1.4)	−0.6 (−0.7 to −0.4)	<0.001	−0.3 (−0.5 to 0)	0.019
Sensation gain								
Present (n = 58)	6.5 (1.6)	−0.9 (1.6)	6.3 (1.7)	0 (1.5)				
Absent (n = 25)	5.6 (1.8)	−1.2 (1.6)	5.7 (2.0)	−0.3 (1.8)	−0.9 (−1.1 to −0.7)	<0.001	0.2 (0 to 0.5)	0.107

Numbers needed to treat (NNT) for more than 50% pain relief was 7.0 (95% CI 4.2-22) in the total population, 3.9 (95% CI 2.3-12) in the IN, and 13 (95% CI 5.2-∞) in the NIN group.

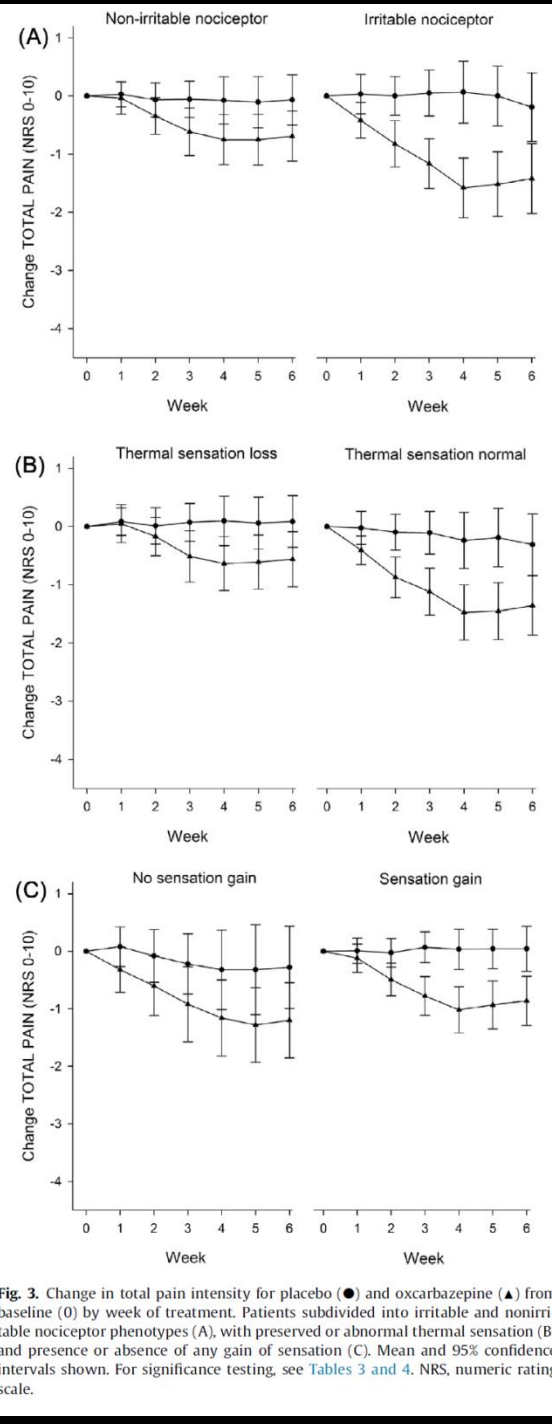


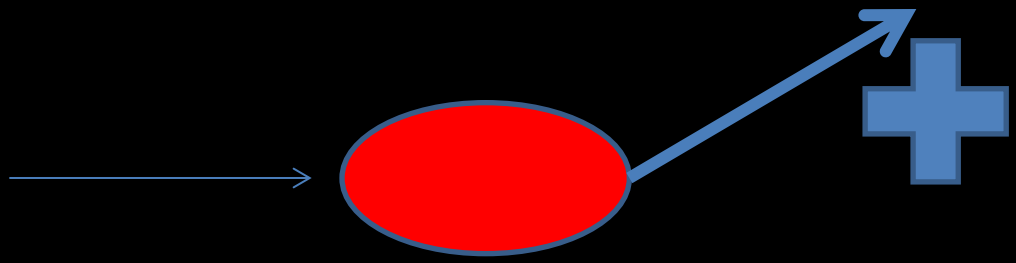
Fig. 3. Change in total pain intensity for placebo (●) and oxcarbazepine (▲) from baseline (0) by week of treatment. Patients subdivided into irritable and nonirritable nociceptor phenotypes (A), with preserved or abnormal thermal sensation (B) and presence or absence of any gain of sensation (C). Mean and 95% confidence intervals shown. For significance testing, see Tables 3 and 4. NRS, numeric rating scale.

IASP PAIN 155 (2014) 2263-2273 PAIN
The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study

Can primary peripheral injuries with spontaneous activity induce a CNS-maintained pain condition?

Definition of central sensitization

Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.



Nociceptive neuron
A central or peripheral neuron of the somatosensory nervous system that is capable of encoding noxious stimuli.

IASP web site (2014)

Note:

Sensitization can include a drop in threshold and an increase in suprathreshold response. Spontaneous discharges and increases in receptive field size may also occur. This is a neurophysiological term that can only be applied when both input and output of the neural system under study are known, e.g., by controlling the stimulus and measuring the neural event. Clinically, sensitization may only be inferred indirectly from phenomena such as hyperalgesia or allodynia. This may include increased responsiveness due to dysfunction of endogenous pain control systems. Peripheral neurons are functioning normally; changes in function occur in central neurons only.

IASP web site (2014)

No nerve injury, normal pain system challenged

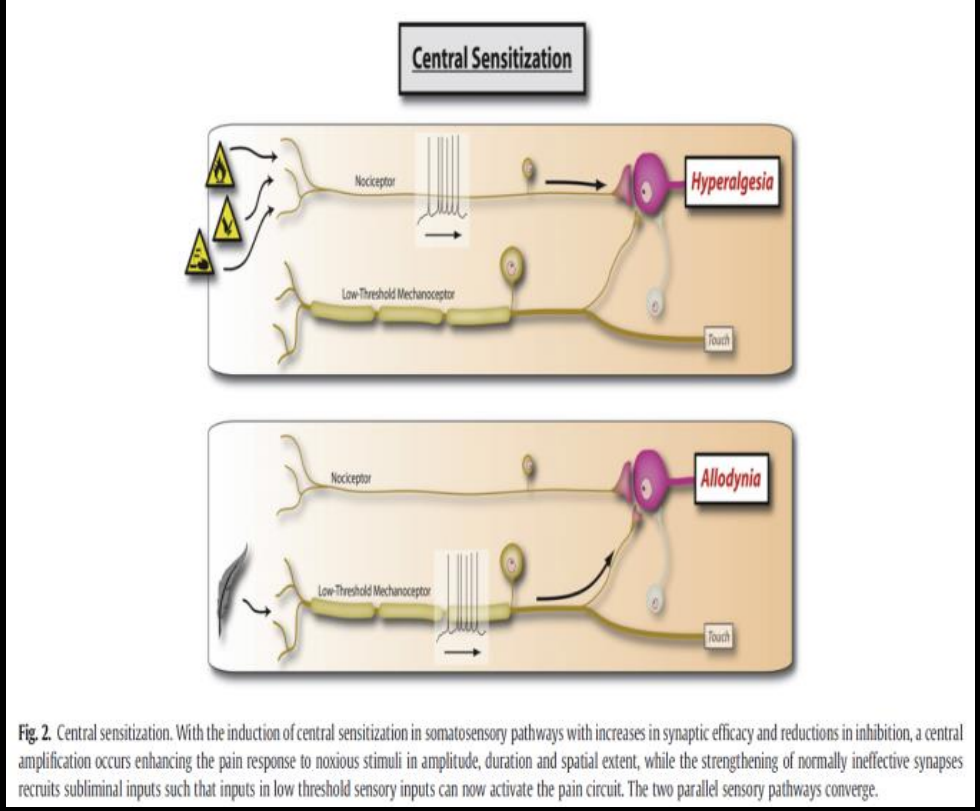


Fig. 2. Central sensitization. With the induction of central sensitization in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge.

Woolf 2011

pains (allodynic and hyperalgesic pain), but there are no demonstrations that central sensitization produces an ongoing discharge in nociceptive CNS neurons that is independent of primary afferent input.

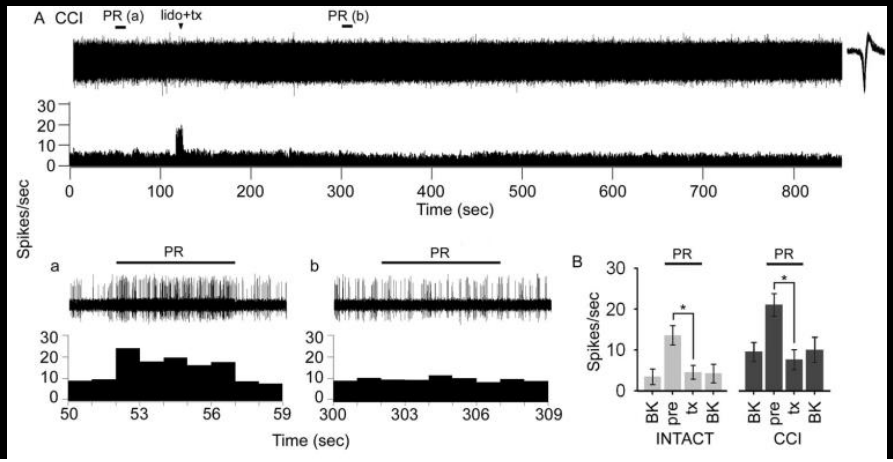
Bennett 2012

Can primary peripheral injuries with spontaneous activity induce a CNS-maintained pain condition?

CCI model

Upregulation of Nav 1.3 (mRNA) in DRG neurons, spinal and thalamic (VPL) neurons

Increased back ground firing and excitability of spinal and VPL neurons



Zhao et al. 2006

Figure 2

Representative recording of spontaneous and evoked activity of a contralateral VPL neuron with a hindlimb receptive field demonstrated spontaneous discharge 10 days after CCI (A). The VPL unit was continuously recorded, and the spinal cord was acutely transected at T6 following application of 2% lidocaine (lido+tx, at t = 120 s). The corresponding unit waveform is shown. Spontaneous background (BK) activity and evoked responses to brush and press (PR, bar) stimuli are shown on an expanded time scale before (a, t = 50–59 sec) and after (b, t = 300–309 sec) cord transection. In CCI animals, spontaneous firing of VPL neurons was unaffected and occurred at a frequency of 5–12 spikes/s following cord transection, but no evoked responses to PR could be elicited (b). Quantification (B) revealed that evoked responses could no longer be elicited after cord transection in intact and CCI (contralateral) groups, and that background activity remained significantly (*$p < 0.05$) elevated in CCI animals before (pre) and after interruption (tx) of ascending afferent barrage compared with intact animals.

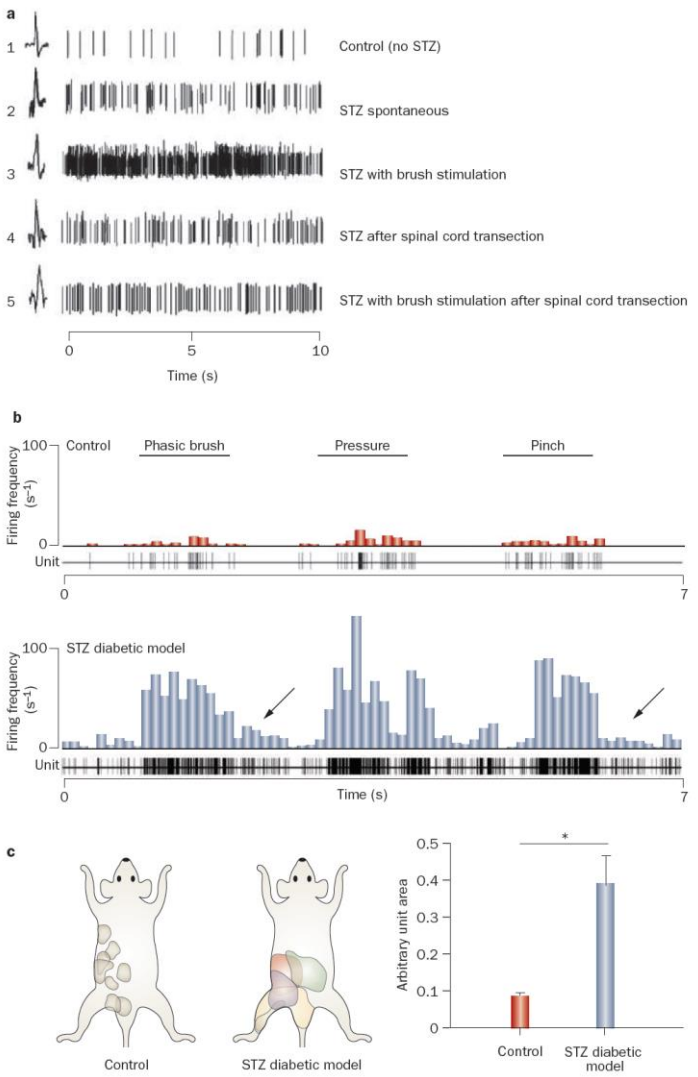


Figure 1 | VPL thalamic neuron activity in a model of painful diabetic neuropathy. **a** | In comparison with wild-type rats (1), animals with STZ-induced diabetes showed increased spontaneous activity in VPL thalamic neurons (2). Complete transection of the cervical spinal cord abolished the response of VPL thalamic neurons to peripheral stimulation (3 and 5), although the rate of spontaneous firing remained higher in STZ-treated animals (4) than in controls (1). **b** | Rats with STZ-induced diabetes, 7 weeks after STZ injection, had substantially larger responses to phasic brush, pressure (1.44 g/mm²) and pinch (538 g/mm²) than did control animals. Afterdischarge only occurred in animals with diabetes (arrows). **c** | The area of the receptive fields of VPL thalamic neurons increased by 457% in rats with STZ-induced diabetes (fields shown in color for clarity) compared with control rats. Graphs show mean ± SE. *Indicates $P<0.05$ (Mann–Whitney rank sum test). Abbreviations: STZ, streptozotocin; VPL, ventral posterolateral. Reprinted from *Brain Res.* **1268**, Fischer, T. Z., Tan, A. M. & Waxman, S. G. Thalamic neuron hyperexcitability and enlarged receptive fields in the STZ model of diabetic pain, 154–161 © (2009), with permission from Elsevier.

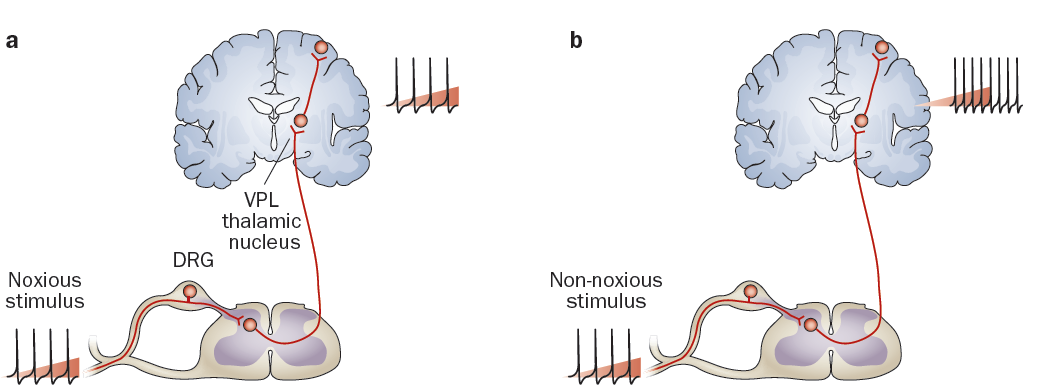


Figure 2 | Models of neuropathic pain. **a** | In nociceptive pain (not associated with diabetes), first-order DRG neurons transmit pain signals to the dorsal horn of the spinal cord. Such signals are relayed by second-order neurons to the VPL thalamic nucleus and, subsequently, transmitted to the primary sensory cortex via third-order neurons. **b** | In pain associated with diabetes, first-order DRG neurons are hyperexcitable, generating impulses in the absence of noxious stimuli. In addition, VPL thalamic neurons generate and amplify pain signals, thereby contributing to chronic pain. Abbreviations: DRG, dorsal root ganglion; VPL, ventral posterolateral.

Box 1 | Evidence of thalamic dysfunction in diabetes mellitus

Animal models of diabetes

- Increase in cerebral blood flow in the thalamus[14]
- Enhanced spontaneous neuronal activity in the thalamus[15]
- Increase in responsiveness of thalamic neurons to peripheral stimulation[15]
- Increase in size of receptive fields of the thalamus[15]

Patients with diabetes mellitus

- Decrease in *N*-acetylaspartate:creatinine ratio in the thalamus of patients with diabetic neuropathy[10]
- Decrease in *N*-acetylaspartate levels in the thalamus of patients with diabetes mellitus and pain[11]
- Increase in thalamic connectivity, as measured by functional MRI, in patients with painful diabetic neuropathy[13]

Fischer & Waxman 2010

Pain, 43 (1990) 287–297
Elsevier

PAIN 01698

Prolonged relief of neuralgia after regional anesthetic blocks. A call for further experimental and systematic clinical studies

Staffan Arnér [a], Ulf Lindblom [b], Björn A. Meyerson [c] and Carl Molander [d]

[a] *Dept. of Anesthesiology and Intensive Care,* [b] *Dept. of Neurology,* [c] *Dept. of Neurosurgery, Karolinska Hospital, Box 60 500, S-104 01 Stockholm (Sweden) and* [d] *Dept. of Anatomy, Karolinska Institute, Box 60 400, S-104 01 Stockholm (Sweden)*

(Received 14 March 1990, revision received 14 June 1990, accepted 20 June 1990)

Summary Thirty-eight consecutive patients with neuralgia after peripheral nerve injury were treated with one or two series of peripheral local anesthetic blocks. All patients experienced an initial total relief of ongoing pain for 4–12 h. Evoked pain (hyperalgesia or allodynia), which occurred in 17 patients, was blocked simultaneously with the spontaneous pain.

In 18 patients the analgesia outlasted the conduction block and there was a period of complete pain relief of 12–48 h in 13 patients and of 2–6 days in the other 5. In 8 patients there was a second phase of analgesia of 4 h to 6 days duration occurring within 12 h of pain recurrence. Thus, mono- or biphasic prolonged complete analgesia occurred in 25 out of 38 patients.

A prolonged analgesia may be the result of a central action of the local anesthetic at the spinal level after intra-axonal incorporation and centripetal axoplasmic transport. To test this hypothesis, an experimental study with [^{3}H]lidocaine was performed in 6 rats. The radioactive local anesthetic was injected into one hind limb foot with the other side serving as a control. Tissue samples from the peripheral nerve, nerve root and the lumbosacral spinal cord segment were analyzed for radioactivity using a scintillation counter technique at various time intervals after the [^{3}H]lidocaine injection. There was a low grade of activity in all samples and no difference between the test side and the control side. Thus these experiments provided no evidence in support of this hypothesis. Various alternative peripheral and central mechanisms are discussed. Further studies specifically directed to these alternatives and with longitudinal controls are prompted.

PAIN® 155 (2014) 1272–1279

PAIN®

www.elsevier.com/locate/pain

Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy

Simon Haroutounian [a,*], Lone Nikolajsen [a,b], Thomas F. Bendtsen [b], Nanna B. Finnerup [a], Anders D. Kristensen [b], Jørgen B. Hasselstrøm [c], Troels S. Jensen [a,d]

No placebo
N=14 (7 PNI+7 DPN)

results are summarized in Table 1. All patients presented sensory disturbances on QST (Fig. 2), and 11 of the 14 patients displayed enhanced temporal summation to pinprick, a surrogate measure for central sensitization. Only 1 patient (patient 11) with a painful

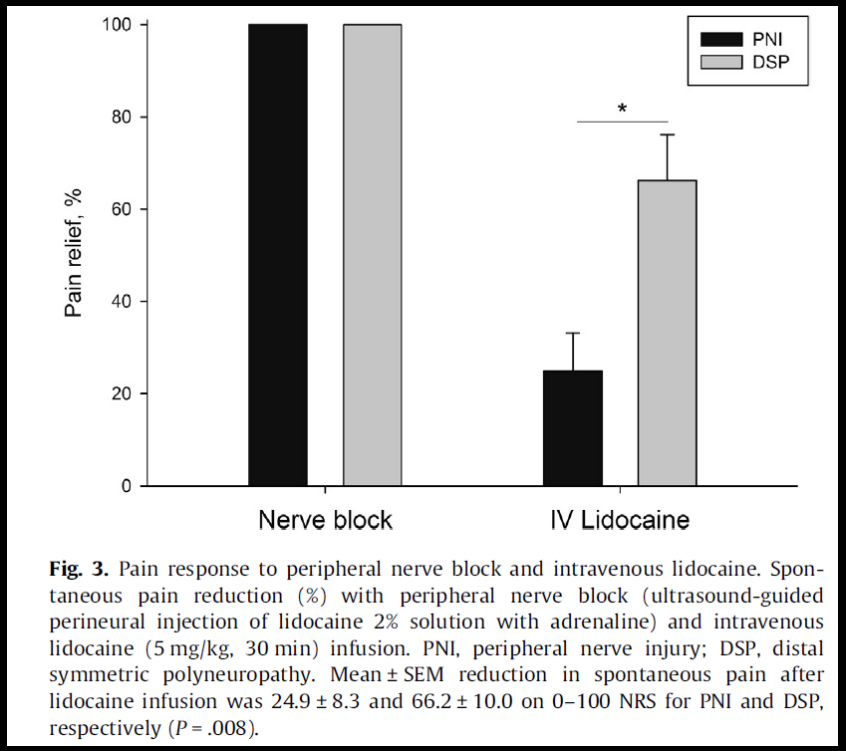


Fig. 3. Pain response to peripheral nerve block and intravenous lidocaine. Spontaneous pain reduction (%) with peripheral nerve block (ultrasound-guided perineural injection of lidocaine 2% solution with adrenaline) and intravenous lidocaine (5 mg/kg, 30 min) infusion. PNI, peripheral nerve injury; DSP, distal symmetric polyneuropathy. Mean ± SEM reduction in spontaneous pain after lidocaine infusion was 24.9 ± 8.3 and 66.2 ± 10.0 on 0–100 NRS for PNI and DSP, respectively ($P = .008$).

PAIN® 155 (2014) 1384–1391

PAIN®

www.elsevier.com/locate/pain

Peripheral nervous system origin of phantom limb pain

Apostol Vaso [a], Haim-Moshe Adahan [b], Artan Gjika [a], Skerdi Zahaj [a], Tefik Zhurda [a], Gentian Vyshka [c], Marshall Devor [d,*]

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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ABSTRACT

Nearly all amputees continue to feel their missing limb as if it still existed, and many experience chronic phantom limb pain (PLP). What is the origin of these sensations? There is currently a broad consensus among investigators that PLP is a top-down phenomenon, triggered by loss of sensory input and caused by maladaptive cortical plasticity. We tested the alternative hypothesis that PLP is primarily a bottom-up process, due not to the loss of input but rather to exaggerated input, generated ectopically in axotomized primary afferent neurons in the dorsal root ganglia (DRGs) that used to innervate the limb. In 31 amputees, the local anesthetic lidocaine was applied intrathecally and/or to the DRG surface (intraforaminal epidural block). This rapidly and reversibly extinguished PLP and also nonpainful phantom limb sensation (npPLS). Control injections were ineffective. For intraforaminal block, the effect was topographically appropriate. The suppression of PLP and npPLS could also be demonstrated using dilute lidocaine concentrations that are sufficient to suppress DRG ectopia but not to block the propagation of impulses generated further distally in the nerve. PLP is driven primarily by activity generated within the DRG. We recommend the DRG as a target for treatment of PLP and perhaps also other types of regional neuropathic pain.

PAIN® xxx (2014) xxx–xxx

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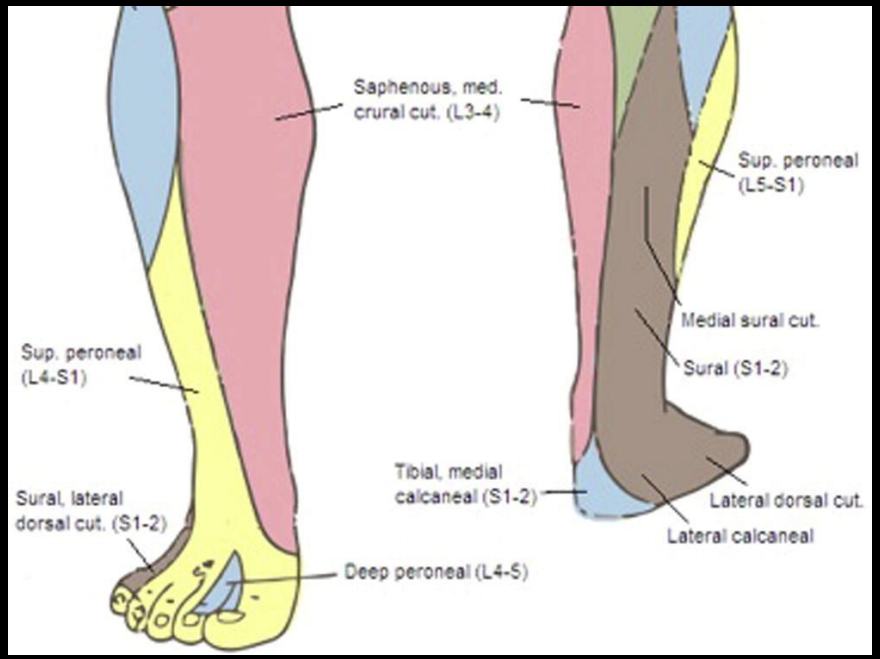
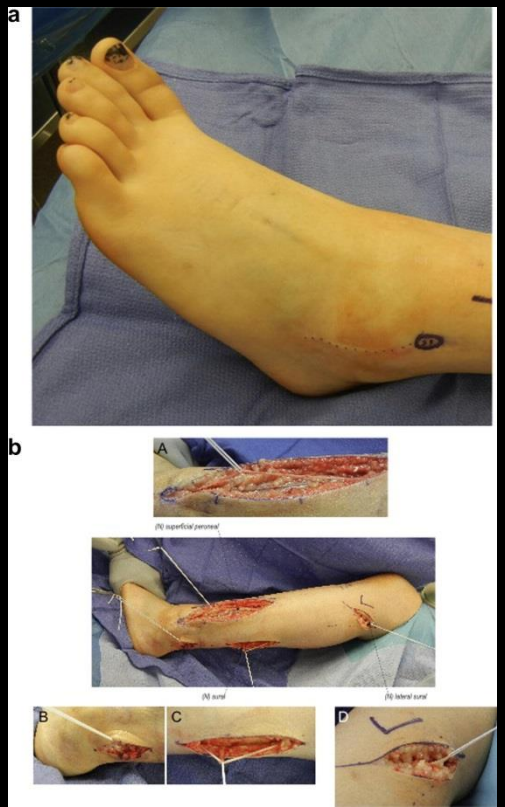
Clinical note

Nerve resection, crush and re-location relieve complex regional pain syndrome type II: A case report

Peter Watson [a,*], Susan Mackinnon [b], Jonathan Dostrovsky [a], Gary Bennett [c], Peter Farran [d], Torie Carlson [d]

Surgery: Resecting and cauterizing the superficial peroneal and sural nerves near the ankle, relocating the proximal nerve stumps into deep muscle around the gastrocnemius/soleus inter-face, and crushing both nerves near the fibular head, for 30 seconds with a hemostat about 35 cm proximal to the ankle.





“We propose that resection should not be done to damaged nerves associated with pain and abnormal sensitivity…”.

Noordenbos, W. and P. D. Wall. J. Neurol. Neurosurg. Psychiat.1981;44: 1068-73.

Challenges:

Study on peripheral nerve destructive surgery in well defined PNeP conditions

How to destroy a peripheral nerve in an optimal way to avoid PNeP?

If you cut damaged nerves consider the possibilities of:

•A painful neuroma will re-form-initial neuroma a risk factor? (if only mechanically sensitive, mobilize to a padded location)

•The DRG as a driver of neuropathic pain-predominant source?

•The CNS as a driver of neuropathic pain-

Evidence for drive sparse, but amplification!

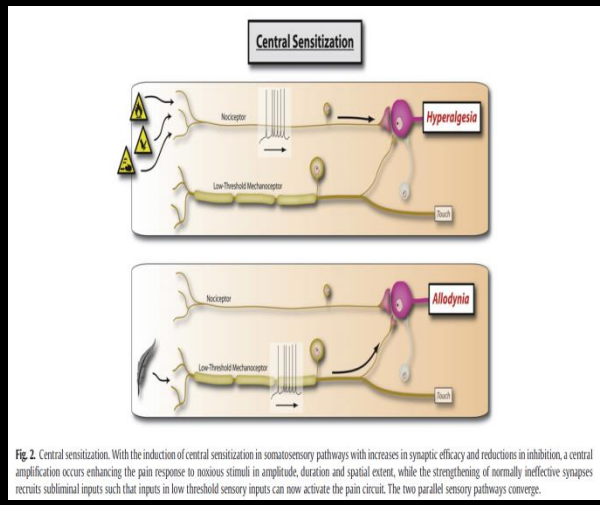
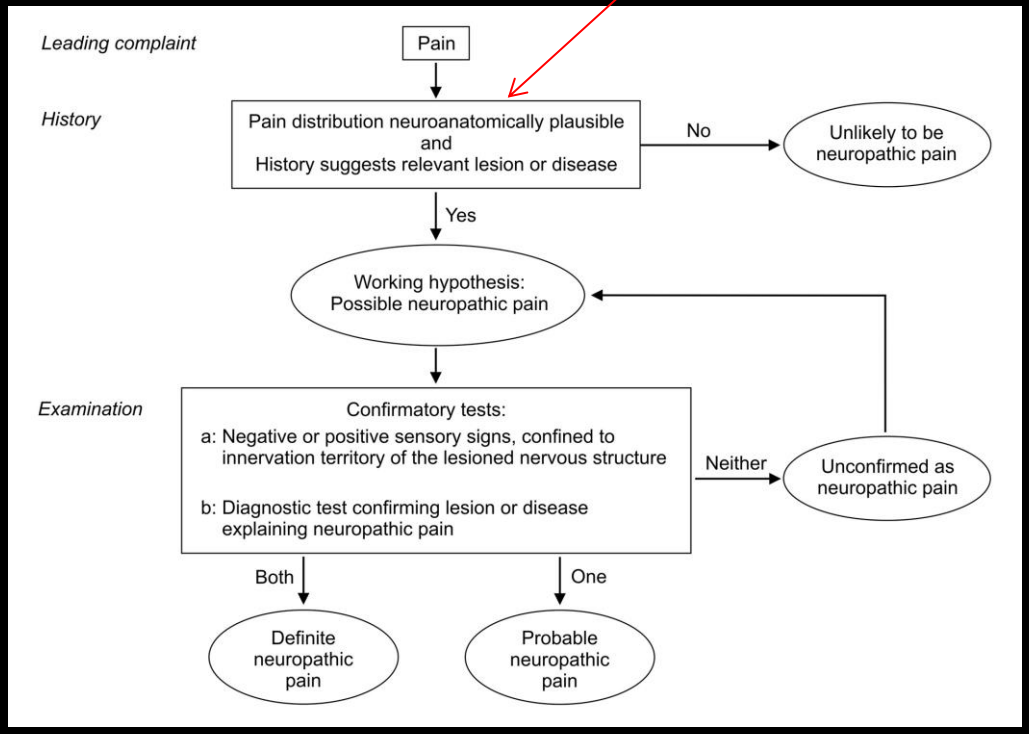
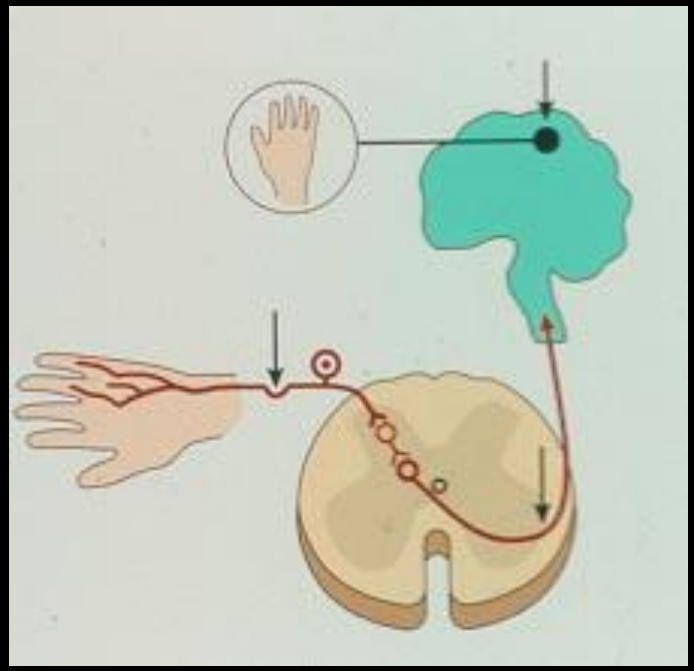


Fig. 2. Central sensitization. With the induction of central sensitization in somatosensory pathways with increases in synaptic efficacy and reductions in inhibition, a central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, while the strengthening of normally ineffective synapses recruits subliminal inputs such that inputs in low threshold sensory inputs can now activate the pain circuit. The two parallel sensory pathways converge.

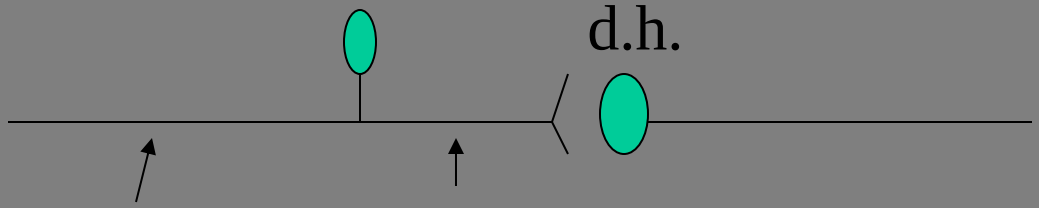
Devor & Tal 2014

All neuropathic pains are projected

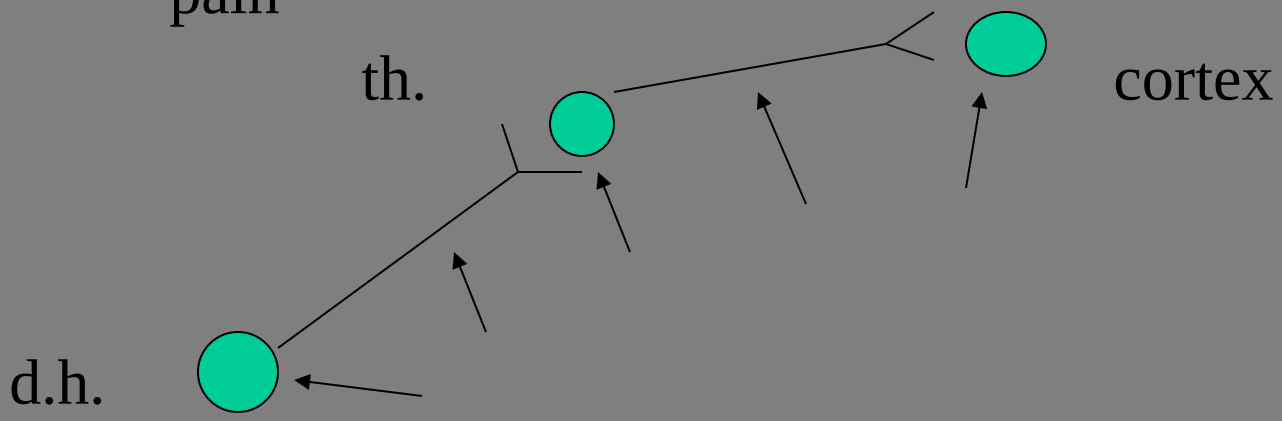




Peripheral: lesion/disease anywhere along the primary afferent system may cause neuropathic pain



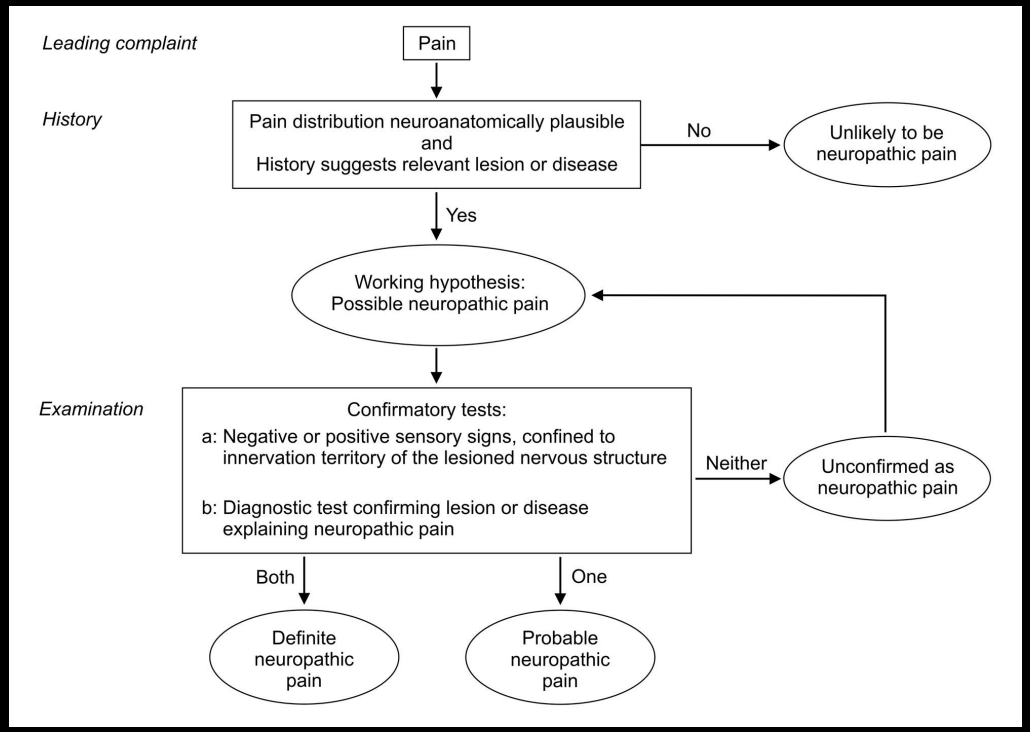
Central: lesion/disease anywhere from the dorsal horn to the cerebral cortex may cause neuropathic pain



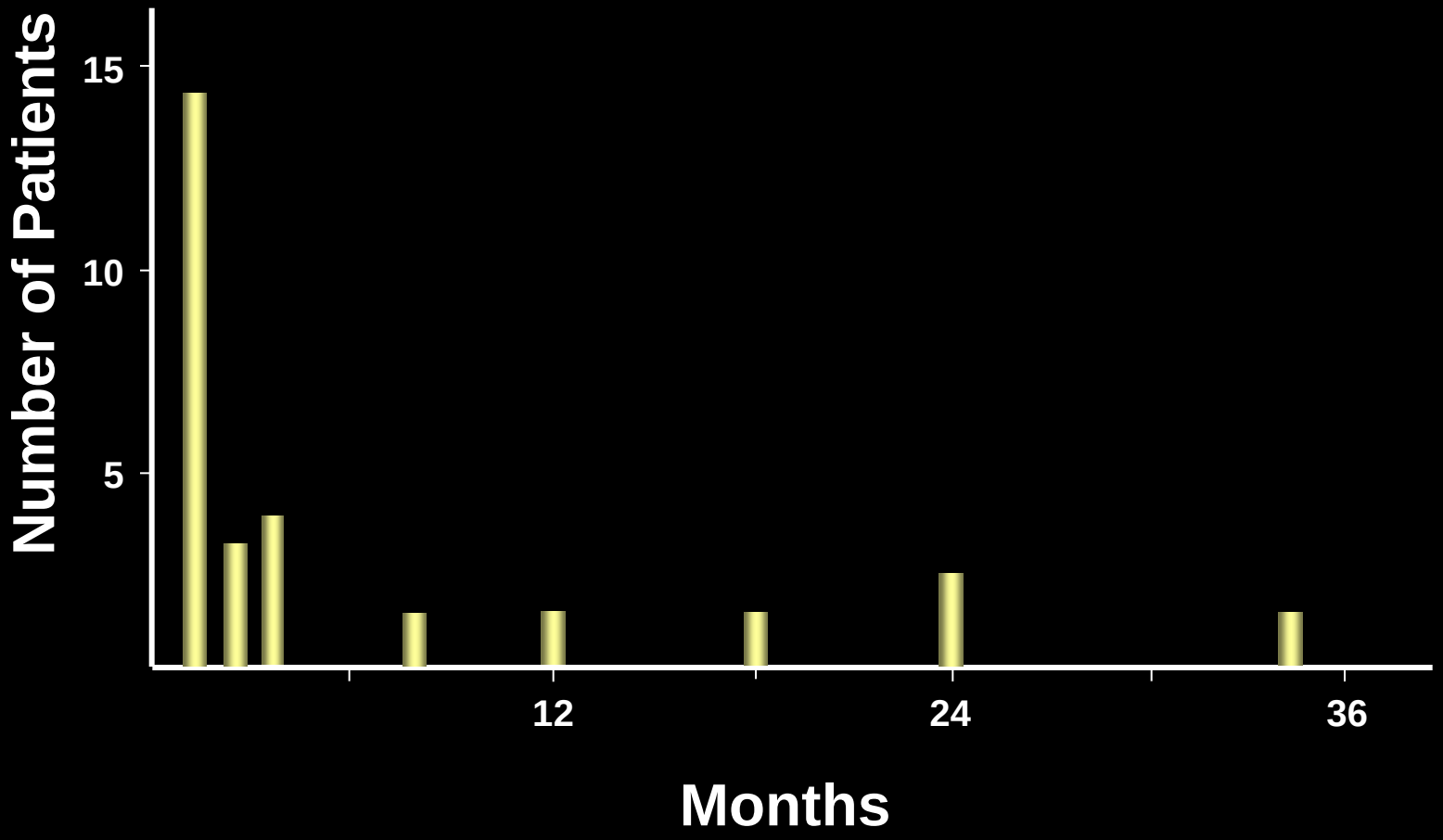
rTMS

Hur small fiber neuropathy kan bjuda sig—att det finns och vem som har det-diagnosmetoder in ccm

Algorithm applicable for somatic, not visceral pains. Are there visceral neuropathic pains?



Latency to Onset of Pain in CPSP



14/27 during the first month

Leijon et al. 1989

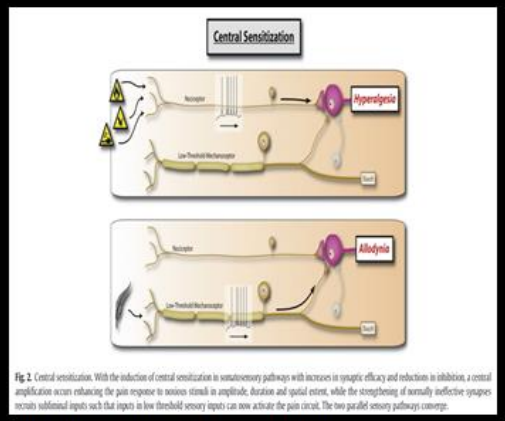
Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine Gabapentin-morphine	Botulinum toxin* Dextromethorphan	Carbamazepine Phenytoin	Capsaicin cream Lacosamide	Duloxetine Gabapentin	Opioids Tramadol[c]
PHN						
Classical trigeminal neuralgia						
Central pai						ds (MS)
				Mexiletine S-ketamine iont. Valproate		SCI)

Pain and anxiety/depression:
Duloxetine: Up to 120 mg/day
Pregabalin: Up to 600 mg/day
TCA: Up to 150 mg/day!!!!

Cyclic antidepressants and the risk of **sudden** cardiac **death**.
Ray WA, Meredith S, Thapa PB, Hall K, Murray KT.
Clin Pharmacol Ther. **2004** Mar;75(3):234-41.

Attal et al. 2010

Brain-brain (net facilitation)



Homo- and heterosynaptic potentiation

Woolf 2011

Loss of inhibition

C-fiber input

Descending net facilitation

Projection neuron

PAIN® 155 (2014) 1384–1391

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www.elsevier.com/locate/pain

Peripheral nervous system origin of phantom limb pain

Apostol Vaso [a], Haim-Moshe Adahan [b], Artan Gjika [a], Skerdi Zahaj [a], Tefik Zhurda [a], Gentian Vyshka [c], Marshall Devor [d,*]

Subject demographics, baseline pain, and results of spinal (intrathecal) block.

Patient no.	Sex/ age, y	Amputation, cause, interval since amputation	Baseline phantom, effect of percussion over stump neuromas (Tinel →), (notes)	Level	Effect of spinal block on phantom and Tinel
1	M/61	R AKA, diabetes, 30 y	PLP lateral foot (severe), npPLS leg below knee, Tinel → PLP	L3–4	PLP, npPLS and Tinel lost, recovery after >3 h
2	F/40	AKA bilateral, trauma, 11 mo	bilateral PLP, bilateral npPLS (numbness, sensation of movement), Tinel → stump pain ("electric")	L3–4	PLP lost, npPLS and Tinel persists, all bilaterally
3	F/65	BKA, scleroderma, 7 days	PLP, npPLS, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost
4	M/52	L AKA, trauma, 3 y, R AKA, vascular, 1 y	L PLP (modest "shooting"), R PLP (severe, "pulsing"), npPLS bilaterally, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost bilaterally
5	F/24	R hip disarticulation, trauma, 2 y	PLP (severe), npPLS (knee to foot), Tinel → PLP	L3–4	PLP, npPLS and Tinel lost
6	M/61	R AKA, vascular, 5 d	PLP ("electric"), npPLS, Tinel → PLP	L2–3	PLP, npPLS and Tinel lost
7	M/48	R AKA, trauma, 10 y	PLP, npPLS, stump (itch + burning), Tinel → PLP (lateral toes)	L4–5	PLP, npPLS and Tinel lost. Stump pain lost
8	M/22	R lateral foot (toes 2–5), trauma, 9 y	PLP (toe 5), npPLS, Tinel → stump pain, scar "cold"	L4–5	PLP, npPLS and Tinel lost
9	M/24	R BKA, trauma, 10 y	PLP (toes 4, 5), npPLS, Tinel → PLP, ongoing stump pain	L4–5	PLP↓, npPLP and Tinel lost
10	M/39	R BKA, trauma, 10 y	PLP, Tinel → PLP + stump pain, ongoing stump pain (cold)	L4–5	PLP, Tinel and stump pain lost
11	M/51	L foot, trauma, 10 y	PLP (sole), npPLS (foot) Tinel → stump pain	L4–5	PLP, npPLS and Tinel lost

R, right; AKA, above knee amputation; PLP, phantom limb pain; npPLS, nonpainful phantom limb sensation; Tinel, evoked Tinel sign; BKA, below knee amputation; L, left.

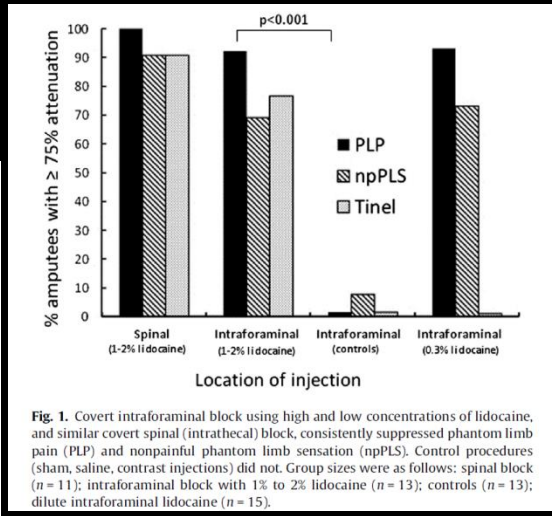

Fig. 1. Covert intraforaminal block using high and low concentrations of lidocaine, and similar covert spinal (intrathecal) block, consistently suppressed phantom limb pain (PLP) and nonpainful phantom limb sensation (npPLS). Control procedures (sham, saline, contrast injections) did not. Group sizes were as follows: spinal block ($n = 11$); intraforaminal block with 1% to 2% lidocaine ($n = 13$); controls ($n = 13$); dilute intraforaminal lidocaine ($n = 15$).

Subject demographics, baseline pain, and results of intraforaminal block.

Patient no.	Sex/ age, y	Amputation, cause, interval since amputation	Baseline phantom, effect of percussion over stump neuromas (Tinel →), notes	Level	Effect of foraminal block on...			Notes
					PLP	npPLS	Tinel →	
1	M/61	R AKA, diabetes, 30 y	PLP lateral foot (severe), npPLS leg below knee, Tinel → PLP	L3	Lost	Lost	Lost	↑ PLP provoked during insertion; result maintained during 5 d infusion
4	M/52	L AKA, trauma, 3 y, R AKA, vascular, 1 y	L PLP (modest "shooting"), R PLP (severe, "pulsing"), npPLS bilaterally, Tinel → stump pain	R–L5	Lost	Lost	Lost	↑ PLP and npPLS provoked during insertion
			7 days later	L–L5	Lost	Lost	Not certain	
5	F/24	R hip disarticulation, trauma, 2 y	PLP, npPLS knee to foot, Tinel → PLP	L4	↓90%	↓90%	Lost	"Shadow" of phantom remains
7	M/48	R AKA, trauma,10 y	PLP, npPLS, stump (itch + burning), Tinel → PLP (lateral toes)	L4	Lost	No change	Lost	
8	M/22	R lateral foot (toes 2–5), trauma, 9 y	PLP (severe in toe 5), npPLS, Tinel → stump pain, scar "cold"	L5	Lost	Lost	Lost	
9	M/24	R BKA, trauma, 10 y	PLP (toes 4, 5), npPLS, ongoing stump pain	L4	Lost	Lost	Lost	
10	M/39	R BKA, trauma, 10 y	PLP ("pinching, like a very tight sock"), npPLS, Tinel → PLP + stump pain, ongoing stump pain (cold)	L5	Lost	Quality changed	Lost	PLP replaced with "pleasant" npPLS
11	M/51	L foot, trauma, 10	PLP (sole), npPLS (foot), Tinel → stump pain	L5	Lost	No change	Not certain	
12	F/55	R BKA, trauma, 17 y	PLP (foot only), npPLS (foot only), Tinel → stump pain	L4	Lost (→ "numb")	↓60%	No change	Foot telescoped to stump, can be moved
			Next day	L5	Not certain	↓, not certain	Lost	
13	M/55	L BKA, trauma, 11 y	PLP, npPLS ("tingling"), Tinel → PLP (in toe 1)	L5	↓60%	Lost	↓50%	Foot telescoped to stump, toes can be moved.
14	M/57	R foot, trauma, 11 y	PLP (toe 1 "bound"), npPLS (toes 2–5), Tinel → PLP (all toes, "electric")	L5	Lost	Only movement lost	To medial toes lost	Foot telescoped to stump, can be moved
			Soon after L5	L4	Still absent	Lost	To lateral toes ↓ 80%	
15	M/52	L at knee, diabetes, 45 d	PLP (toe 1 and ankle), npPLS (whole leg), Tinel → stump pain	L4	Lost	Lost	Lost	Result maintained during 12 d infusion
16	F/77	L medial toe (toe 1), diabetes, 17 d	PLP ("sharp"), npPLS, Tinel → stump pain	L5	Lost	Not certain	Lost	Result maintained during 10 d infusion

R, right; AKA, above knee amputation; PLP, phantom limb pain; npPLS, nonpainful phantom limb sensation; Tinel, evoked Tinel sign; BKA, below knee amputation; L, left.