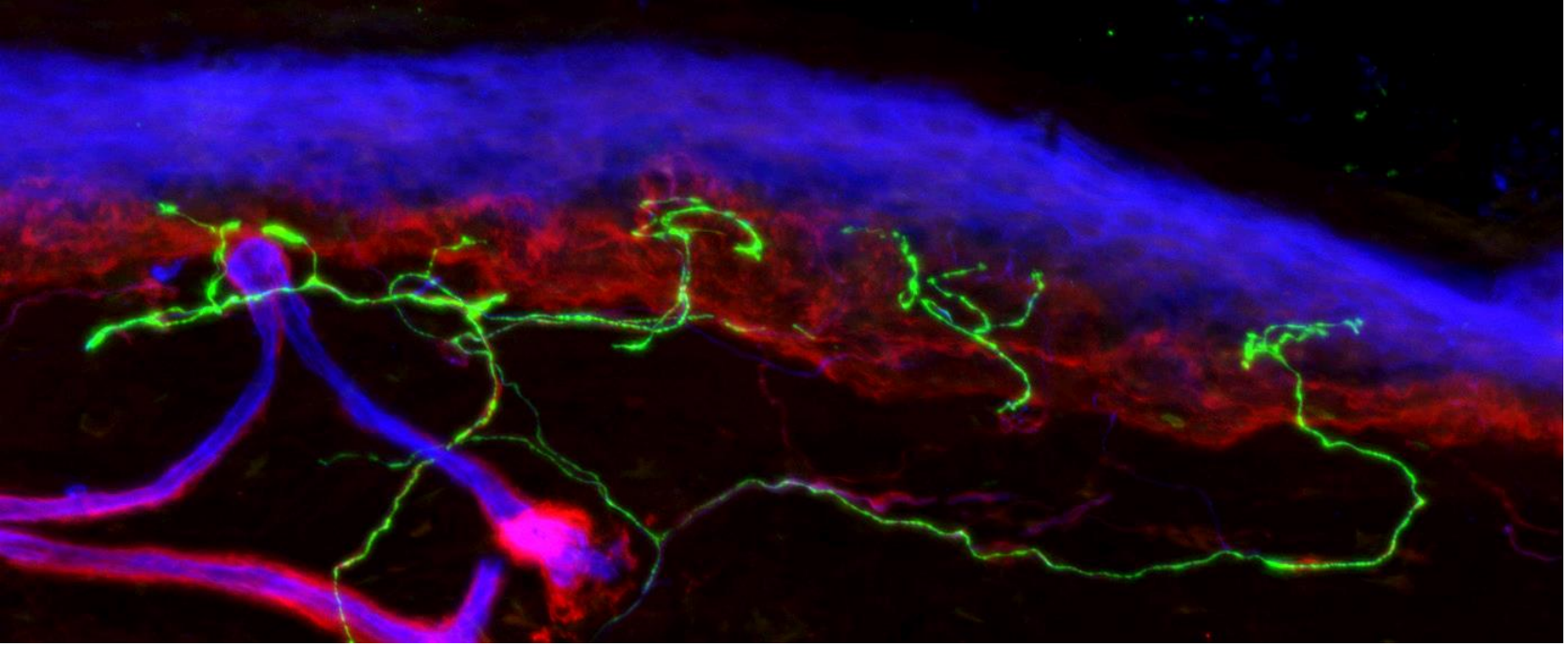


Maria Nolano

Skin Biopsy Lab
ICS MAUGERI – IRCCS di Telese Terme

Dipartimento di Neuroscienze e Scienze riproduttive ed odontostomatologiche
Università Federico II di Napoli

Trattamento del dolore neuropatico

Regionale SIN Campania
CRONICITÀ NELLE MALATTIE NEUROLOGICHE
Salerno, 14 dicembre 2018

DOLORE NEUROPATICO CRONICO

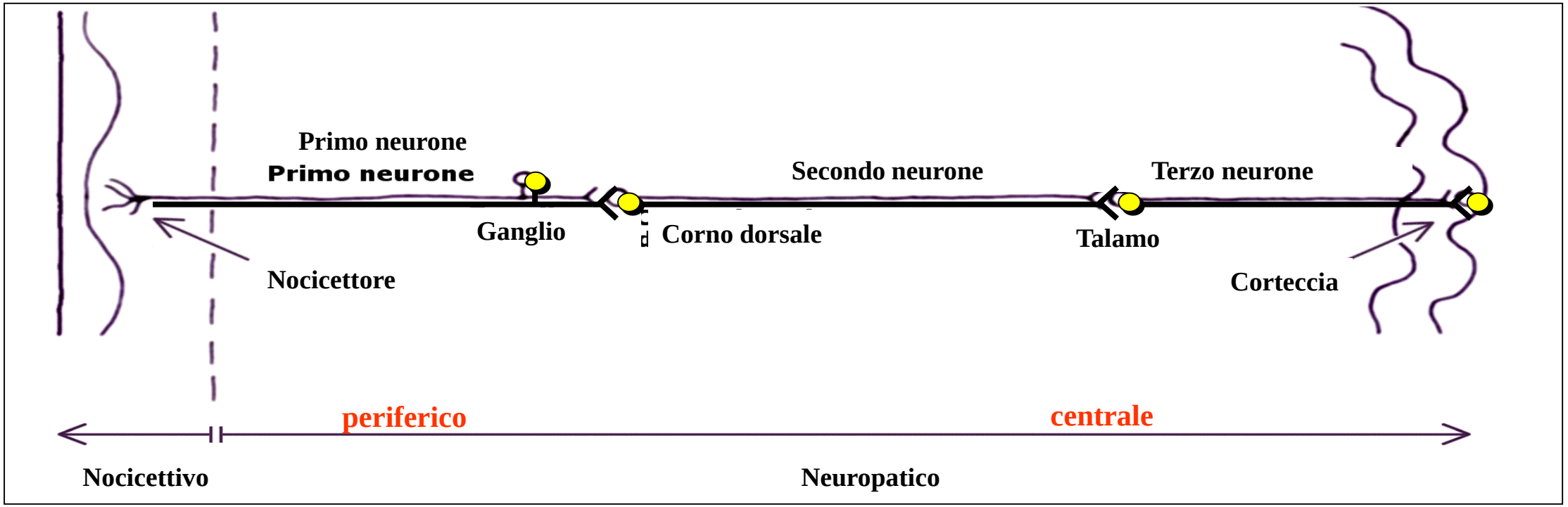
- ✓ Presente nel 6.9 – 10.0 % della popolazione.
- ✓ Condizione cronica che rappresenta un onere significativo per pazienti, società e sistema sanitario
- ✓ Interferisce con umore, funzioni cognitive, QoL, attività sociali

Destinato ad aumentare per:

- ➢ aumento dell'invecchiamento della società
- ➢ aumento dell'obesità
- ➢ aumento della sopravvivenza dopo cancro

Viene definito neuropatico il dolore causato

da “lesione o malattia” del sistema “somatosensoriale”



Definition

Pain is called neuropathic when it arises as the direct result of a disease or lesion of the central and/or peripheral somatosensory nervous system.

Task Force Neurologica (Treede et al. Neurology 2008)

POSITIVE SYMPTOMS AND SIGNS

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Paroxysmal pain	Spontaneous activity in C-fibres
Superficial pain	Spontaneous activity in Aδ- and C-fibres
Deep pain	Spontaneous activity in articular/muscular nociceptors
Paraesthesia	Spontaneous activity in Aβ-fibres

SIGNS (EVOKED PAIN)	PHYSIOPATHOLOGICAL MECHANISMS
Cold hyperalgesia	Central sensitization/loss of central inhibition
Heat hyperalgesia	Peripheral sensitization
Punctate hyperalgesia	Central sensitization mediated by Aδ-fibres
Mechanical allodynia	Heterosynaptic central sensitization
Temporal summation of pain	Homosynaptic central sensitization
After-sensations	Homosynaptic central sensitization

NEUROPATHIC PAIN SYNDROMES

Coexistence of negative symptoms/signs (loss-of-function of the somatosensory system) and positive symptoms/signs (gain-of-function of the somatosensory system)

SYMPTOMS	PHYSIOPATHOLOGICAL MECHANISMS
Hypalgesia	Aδ-fibres lesion

SIGNS	PHYSIOPATHOLOGICAL MECHANISMS
Tactile hypesthesia	Aβ-fibres lesion
Hypopallesthesia	Aβ-fibres lesion
Thermal hypesthesia	Aδ- and C-fibres lesion
Punctate hypesthesia	Aδ-fibres lesion

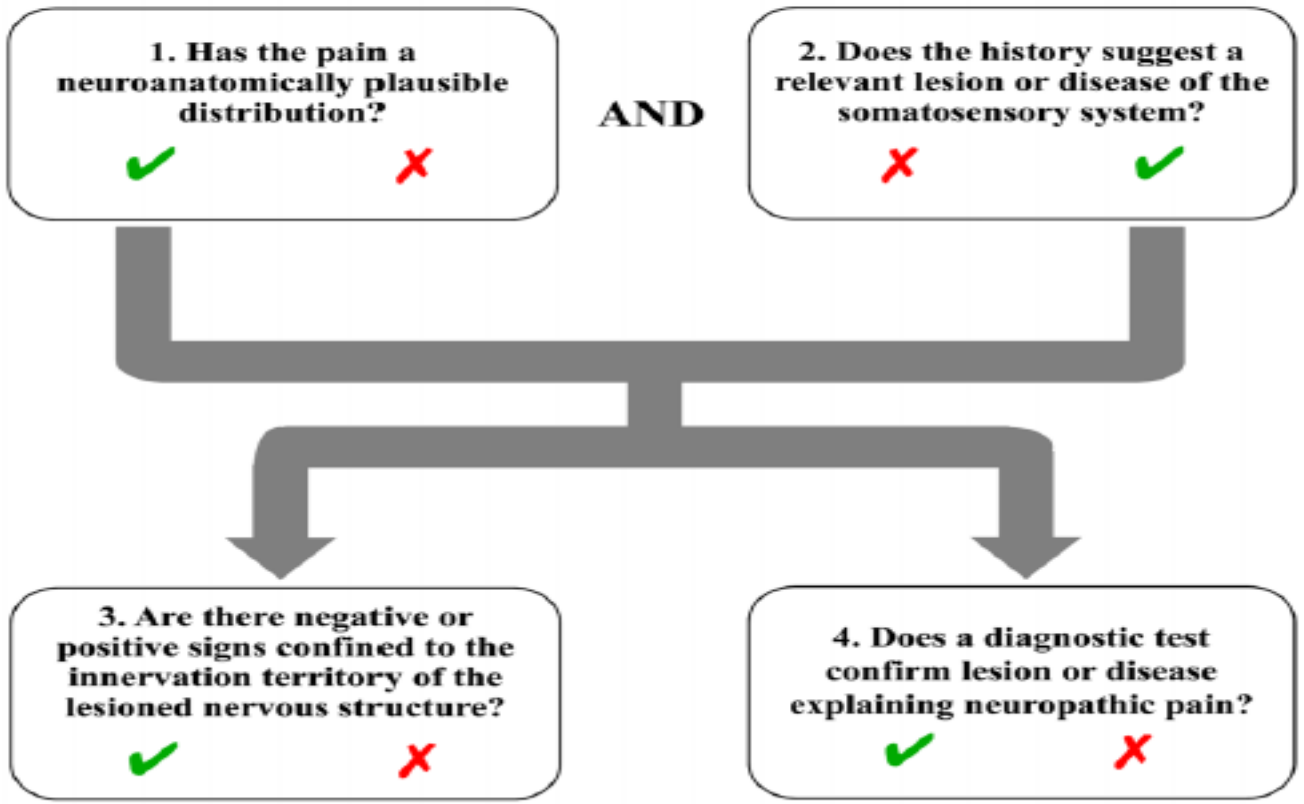
NEGATIVE SYMPTOMS AND SIGNS

Table 4 Screening tools for NP

Tool	Administration	NP descriptors items	Clinical examination items	Validated for	Sensitivity (%)	Specificity (%)	Ref
LANSS	CA	5 items with yes/no answer	2	PNP	83[A]; 85[B]	87[A]; 80[B]	13
S-LANSS	SAQ	5 items with yes/no answer	None		74	78	14
NPQ	SAQ	12 scored (0–100) items	None	PNP	66.6	74.4	15
DN4	CA	7 items with yes/no answer	3	PNP, CNP	82.9	89.9	16
DN4-Interview	SAQ	7 items with yes/no answer	None				
ID-Pain	SAQ	6 items with yes/no answer	None	PNP	Not assessed	Not assessed	17
PainDETECT	SAQ	7 scored (0–5) items	None	PNP	85	80	18
StEP	CA	6 items with yes/no answer	10	NLBP	92	97	19

Magrinelli F, *et al*. *Pract Neurol* 2013;**13**:292–307.

PATIENT COMPLAINT: PAIN



HOW TO?

If question 1 and/or question 2 ✗
UNLIKELY NEUROPATHIC PAIN:
disregard questions 3 and 4

If questions 1 and 2 ✔
POSSIBLE NEUROPATHIC PAIN:
go ahead to questions 3 and 4

If questions 1 and 2 ✔
but questions 3 and 4 ✗
UNCONFIRMED NEUROPATHIC PAIN

If questions 1, 2 and 3 ✔
or questions 1, 2 and 4 ✔
PROBABLE NEUROPATHIC PAIN

If questions 1, 2, 3 and 4 ✔
DEFINITE NEUROPATHIC PAIN

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Magrinelli F, *et al*. *Pract Neurol* 2013;**13**:292–307.

Neuropathic Pain syndromes
according to the site of damage of the somatosensory system

Asymmetrical
(focal and multifocal) lesions in the peripheral nervous system

- Entrapment mononeuropathies (carpal tunnel syndrome, ulnar nerve entrapment at the elbow, meralgia paraesthetica due to injury to lateral femoral cutaneous nerve, peroneal nerve entrapment at the fibular head)
- Post-traumatic and postsurgical mononeuropathies
- Phantom limb pain
- Cervical, thoracic and lumbosacral radiculopathies
- Trigeminal neuralgia
- Diabetic monoradiculopathies and mononeuropathies
- Postherpetic neuralgia
- Brachial and lumbosacral plexopathies (inflammatory, traumatic, brachial plexus avulsion, neoplastic, radiotherapy, diabetic lumbosacral radiculoplexus neuropathies)
- Vasculitic multineuropathies

Symmetrical lesions of peripheral nervous system (painful polyneuropathies)

- Diabetic distal symmetrical and small fibre polyneuropathies
- Metabolic (alcohol-related, secondary to vitamin deficiency) neuropathies
- Malignancy-associated neuropathies
- Immune-mediated polyneuropathies
- Neuropathy secondary to chemotherapy
- HIV/AIDS-related polyneuropathy
- Hereditary sensory neuropathies, amyloid neuropathies
- Neuropathy in Fabry's disease

Lesion in the central nervous system

- Spinal cord lesions (injury, infarction, inflammatory, spondylotic)
- Central poststroke pain
- Multiple sclerosis-related NP

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Magrinelli F, et al. Pract Neurol 2013;13:292–307. doi:10.1136/practneurol-2013-000536

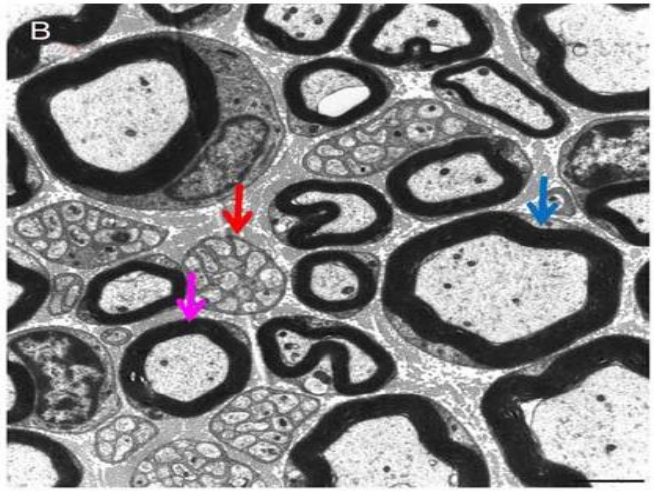
NEUROPATIE DELLE PICCOLE FIBRE

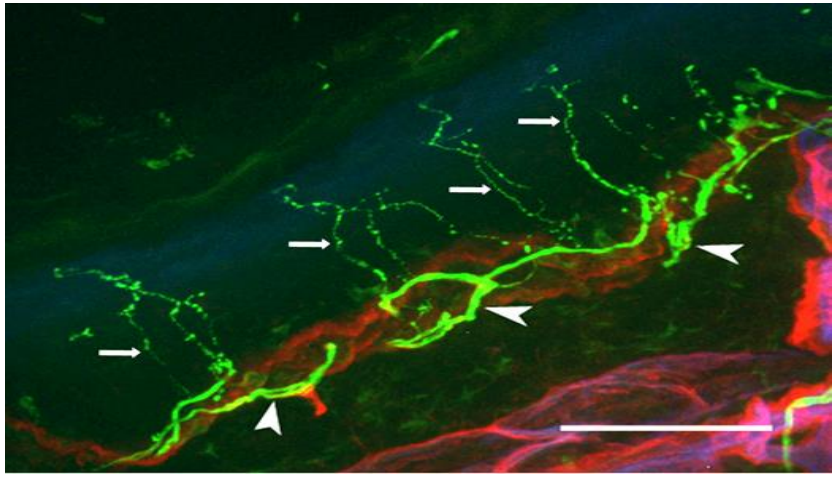
« Coinvolgimento selettivo o prevalente delle fibre mieliniche di piccolo calibro e amieliniche »

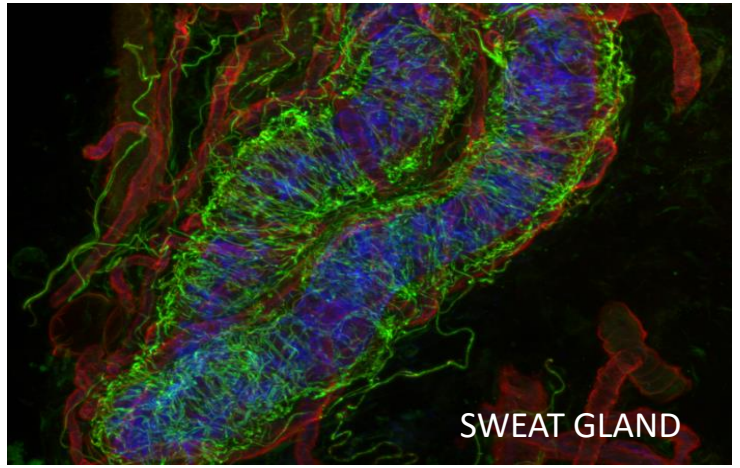
✓Normalità della forza muscolare

✓Normalità dei riflessi osteo-tendinei

✓Normalità delle indagini elettrofisiologiche di routine







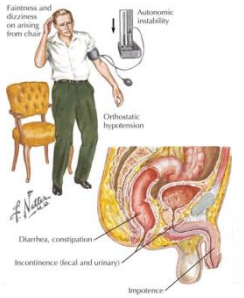
CARATTERISTICHE CLINICHE

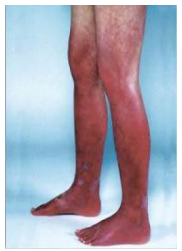
DISTURBI SENSITIVI

- Dolore: peggiora nelle ore notturne, spesso urente
- Intolleranza al contatto con indumenti o lenzuola
- Sindrome delle gambe senza riposo
- Sensazione di intorpidimento, di “fascia” o di “freddo”

SINTOMI DI DISFUNZIONE AUTONOMICA

- Ipo o iperidrosi, diarrea o stipsi, gastroparesi
- Incontinenza o ritenzione urinaria
- Visione offuscata, arrossamenti facciali transitori
- Disfunzione sessuale, disturbi vasomotori acrali





✓ Dolore urente

✓ Freddo doloroso

✓ Prurito

✓ Stretta dolorosa

✓ Dolore lancinante

ALGORITHM FOR DIAGNOSIS OF SMALL FIBRE NEUROPATHY

Clinical suspicion
- Symptoms – somatic sensory or autonomic
- Signs- loss of thermal and pinprick sensation

↓

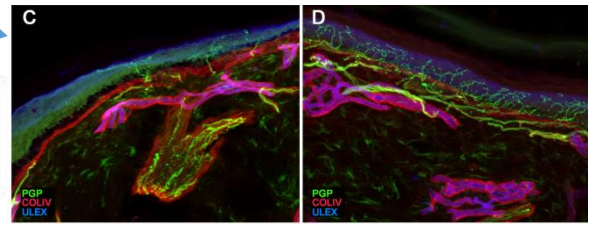
Nerve conduction studies → abnormal → Large fibre neuropathy

normal ↓

Quantitative sensory testing
Skin biopsy → normal → Investigate for CNS pathology

abnormal ↓

Investigate for causes of small fibre neuropathy (Table 2)



If no cause found ↓

Idiopathic small fibre neuropathy

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Themistocleous AC, et al. Pract Neurol 2014;14:368–379

Table 1 Causes of small fibre neuropathy

Primary	Secondary
Idiopathic	Metabolic
▶ Idiopathic small fibre neuropathy	▶ Impaired glucose tolerance
▶ Burning mouth syndrome	▶ Diabetes mellitus
	▶ Rapid glycaemic control
	▶ Vitamin B12 deficiency
	▶ Dyslipidaemia
	▶ Hypothyroidism
	▶ Chronic kidney disease
Hereditary/genetic	Infections
▶ $Na_v1.7$ mutations	▶ HIV
▶ $Na_v1.8$ mutations	▶ Hepatitis C
▶ Familial amyloid polyneuropathy	▶ Influenza
	Toxins and drugs
▶ Fabry's disease	▶ Anti-retrovirals
▶ Tangier's disease	▶ Antibiotics—metronidazole, nitrofurantoin, linezolid
	▶ Chemotherapy—bortezomib
	▶ Flecainide
	▶ Statin
	▶ Alcohol
	▶ Vitamin B6 toxicity
	Immune mediated
	▶ Coeliac disease
	▶ Sarcoidosis
	▶ Sjögren's syndrome
	▶ Rheumatoid arthritis
	▶ Systemic lupus erythematosus
	▶ Vasculitis
	▶ Inflammatory bowel disease
	▶ Paraneoplastic
	▶ Monoclonal gammopathy/amyloid

Note that a number of these conditions may present as a small fibre neuropathy and then evolve to include large fibres.

Review

Painful Na-channelopathies: an expanding universe

Stephen G. Waxman[1,2]

Review

Trends in Molecular Medicine July 2013, Vol. 19, No. 7

Table 1. Human painful Na-channelopathies

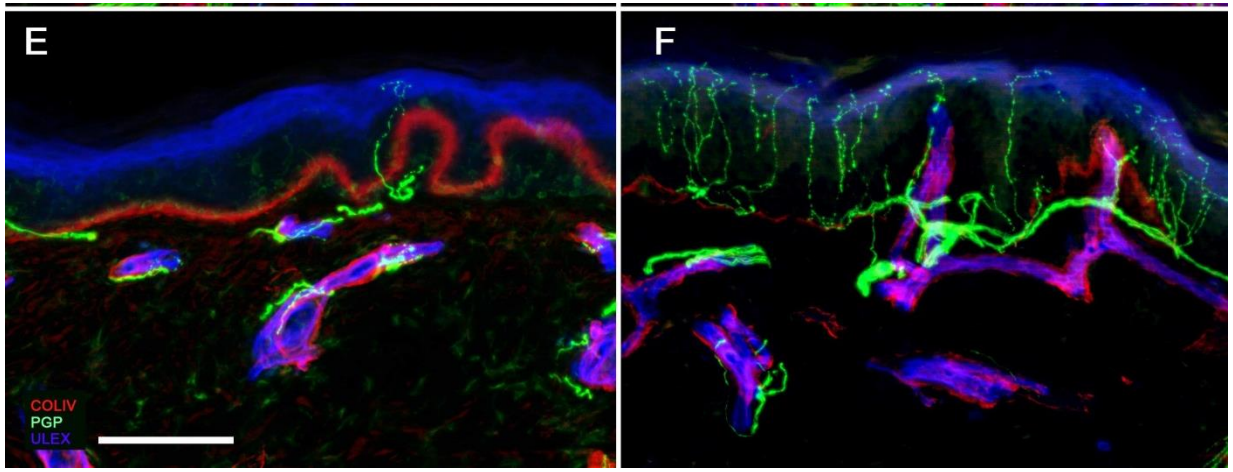
Disorder	Channel	Mutation	Pattern	Refs
Inherited erythromelalgia	$Na_V1.7$	Gain-of-function, primarily enhanced activation	Distal limbs	[7,8]
PEPD	$Na_V1.7$	Gain-of-function, primarily impaired fast-inactivation	Perirectal, periorbital, perimandibular	[9]
Overlap syndrome	$Na_V1.7$	Enhanced activation + impaired fast-inactivation	Mixed	[10]
Channelopathy associated insensitivity to pain	$Na_V1.7$	Loss-of-function		[11–13]
Painful peripheral neuropathies	$Na_V1.7$	Gain-of-function, multiple effects on channel	Early pain usually distal	[19]
Painful peripheral neuropathies	$Na_V1.8$	Gain-of-function, multiple effects on channel	Early pain usually distal	[21]

Review

Painful and painless channelopathies

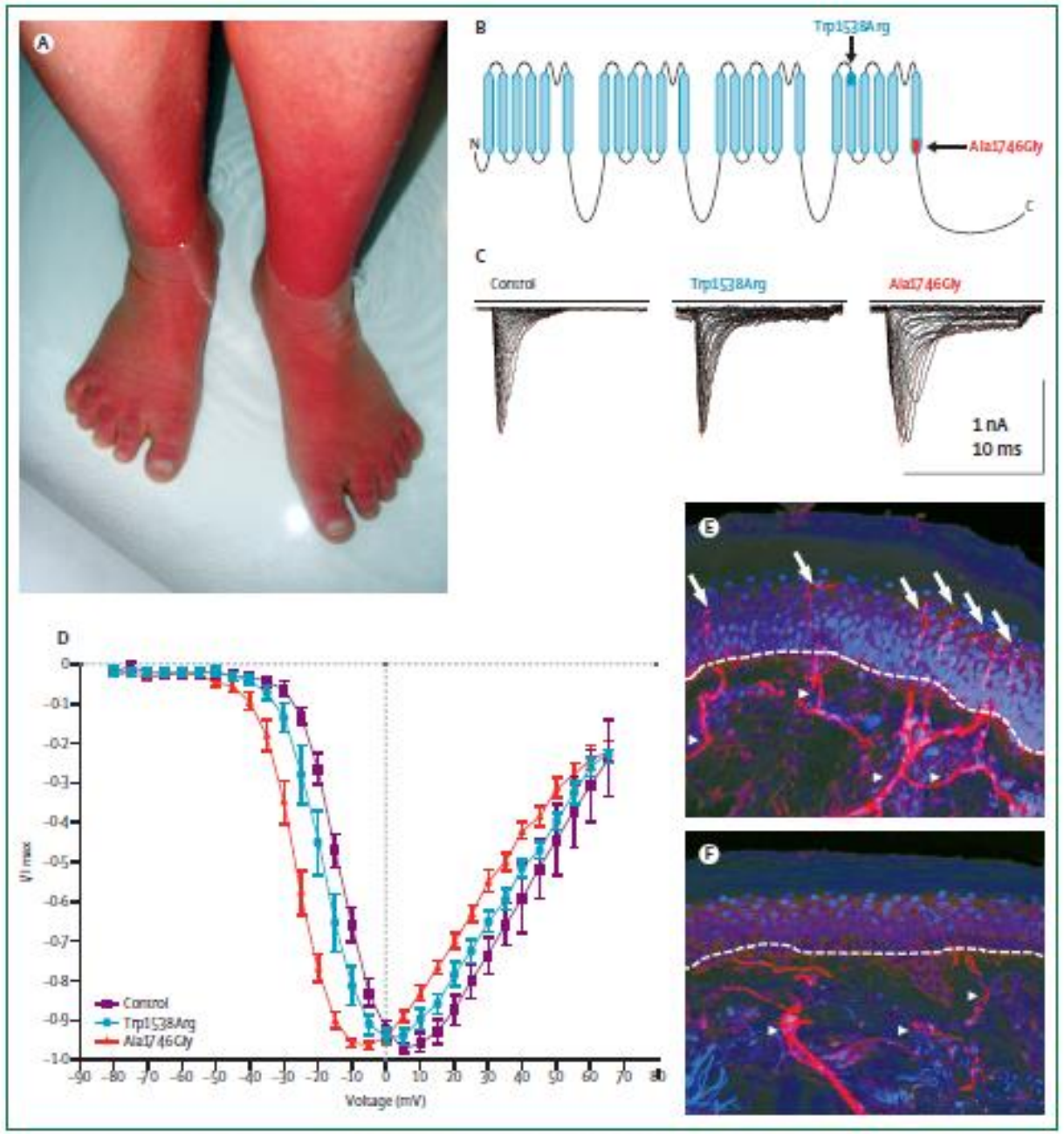
David L H Bennett, C Geoffrey Woods

The discovery of genetic variants that substantially alter an individual's perception of pain has led to a step-change in Lancet Neurol 2014



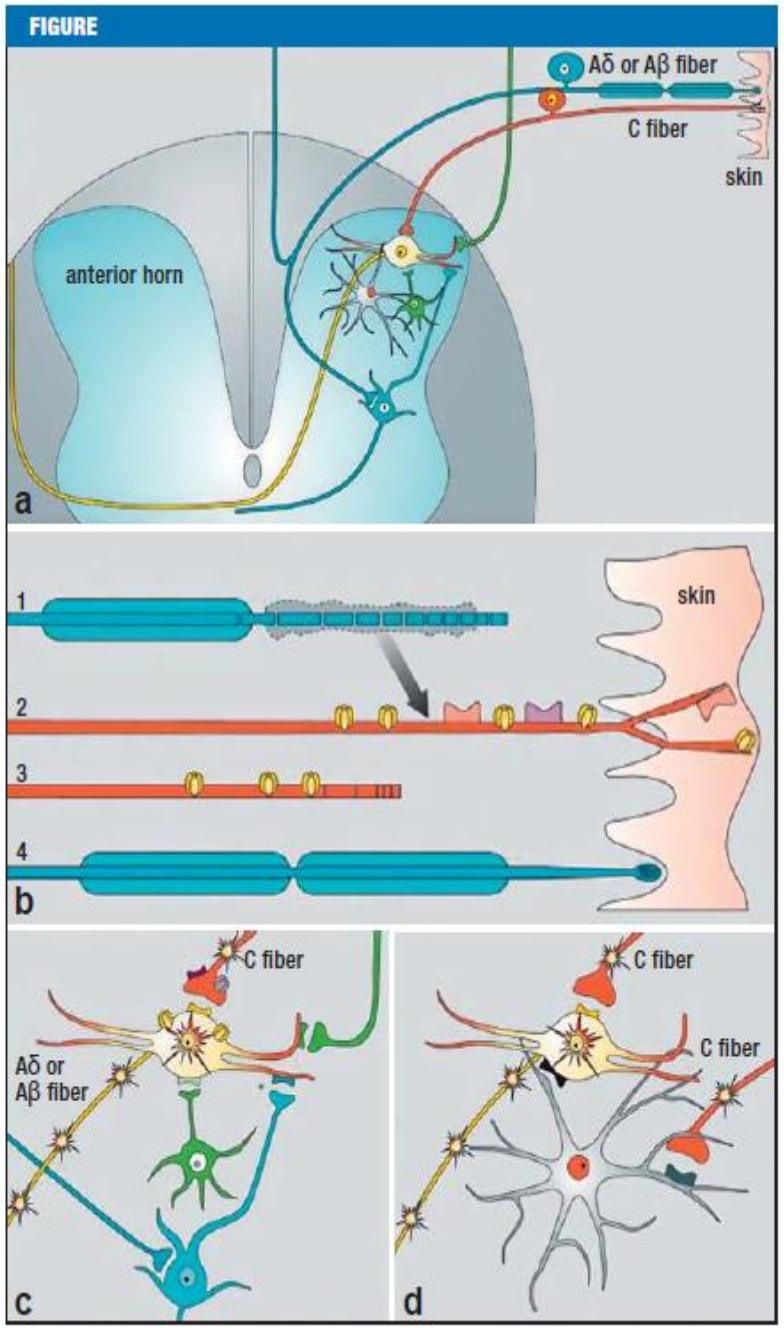
CASE REPORT

A novel *SCN9A* splicing mutation in a compound heterozygous girl with congenital insensitivity to pain, hyposmia and hypogeusia

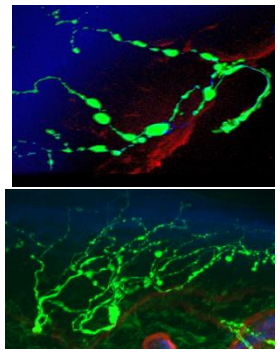


Istituti Clinici Scientifici Maugeri | SkinBiopsyIta | JPNS Journal of the Peripheral Nervous System
The Official Journal of The Peripheral Nerve Society

- **Diagnosticare il dolore neuropatico**
- **Cercare e trattare la causa**
- **Trattare il dolore neuropatico**



Pathophysiological mechanisms of neuropathic pain (modified from Baron et al., Lancet Neurol 2010 [4])



I MECCANISMI TARGET DEL DOLORE NEUROPATICO

Il danno nervoso altera le proprietà neurofisiologiche del neurone afferente

Il nervo danneggiato, i fenomeni degenerativi e rigenerativi danno luogo a scariche ectopiche responsabile del dolore spontaneo

L'attività ectopica è mantenuta da diversi fattori tra cui aumentata espressione di canali del sodio voltaggio dipendenti e canali TRP Questi canali possono esssere modulati dalla carbamazepina, lidocaina e capsaicina.

Una ipereccitabilità a carico dei neuroni del midollo intensifica il dolore spontaneo ed è alla base di iperagesia e allodinia meccanica. Questa sensibilizzazione centrale è modulata da farmaci come i gabapentinoidi e dagli oppioidi.

La trasmissione dell'impulso nocicettivo è fisiologicamente modulata da sistemi inibitori discendenti. Questo effetto è potenzianto dagli antidepressivi

Table 1 – Recommended pharmacotherapy for neuropathic pain.

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Antidepressants				
Amitriptyline, Clomipramine Imipramine Nortriptyline[b], Desipramine[b],	Monoamine reuptake inhibition; sodium channel blockade; anticholinergic effects	3.6 (3.0–4.4)	Somnolence, anticholinergic effects and weight gain	Cardiac disease, glaucoma, prostatic adenoma, seizure; high doses should be avoided in adults older than 65 years of age
Duloxetine Venlafaxine	Serotonin and norepinephrine reuptake inhibition	6.4 (5.2–8.4)	Nausea, abdominal pain and constipation, hypertension at high dosages for venlafaxine	Hepatic disorder (duloxetine) Hypertension Cardiac disease Use of tramadol
Antiepileptics				
Gabapentin Gabapentin extended-release (ER)/enacarbil[b] Pregabalin	Act on Alpha2-Delta subunit of voltage-gated calcium channels, which decreases central sensitization	6.3 (5.0–8.4) for gabapentin 8.3 (6.2–13) for gabapentin ER/ enacarbil 7.7 (6.5–9.4) for pregabalin	Sedation, dizziness, peripheral edema and weight gain	Reduce dose in renal insufficiency
Topical agents				
Lidocaine 5% plasters	Sodium channel blockade	NA	Local erythema, itching and rash	None
Capsaicin high concentration patches (8%)	Transient receptor potential vanilloid type 1 agonist (TRPV1)	10.6 (7.4–19)	Pain, erythema, itching; rare cases of high blood pressure (initial increase in pain)	No overall impairment of sensory evaluation after repeated applications, caution in progressive neuropathy
Opioids				
Tramadol	Mu receptor agonist; Monoamine reuptake inhibition	4.7 (3.6–6.7)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, use of antidepressant in elderly patients
Strong opioids (e.g. morphine, oxycodone, methadone)	Mu receptor agonist; oxycodone may also cause kappa receptor antagonism	4.3 (3.4–5.8)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, risk of misuse on long-term use
Neurotoxins				
Botulinum toxin type A	Acetylcholine release inhibitor and neuromuscular blocking agent Potential effects on mechano-transduction and central effects in neuropathic pain	1.9 (1.5–2.4)[c]	Pain at injection site	Known hypersensitivity and infection of the painful area

Pharmacological treatment of neuropathic pain: The latest reccommendation.

Attal N. Revue Neurologique 2018

Le linee guida della IASP NeuroSPIG, EFNP, CARE, NICE concordano su 3 classi di farmaci come prima linea

- **Antidepressivi Triciclici**
- **SNRI**
- **Anticonvulsivanti Alfa-2-delta ligandi**

Antidepressivi triciclici

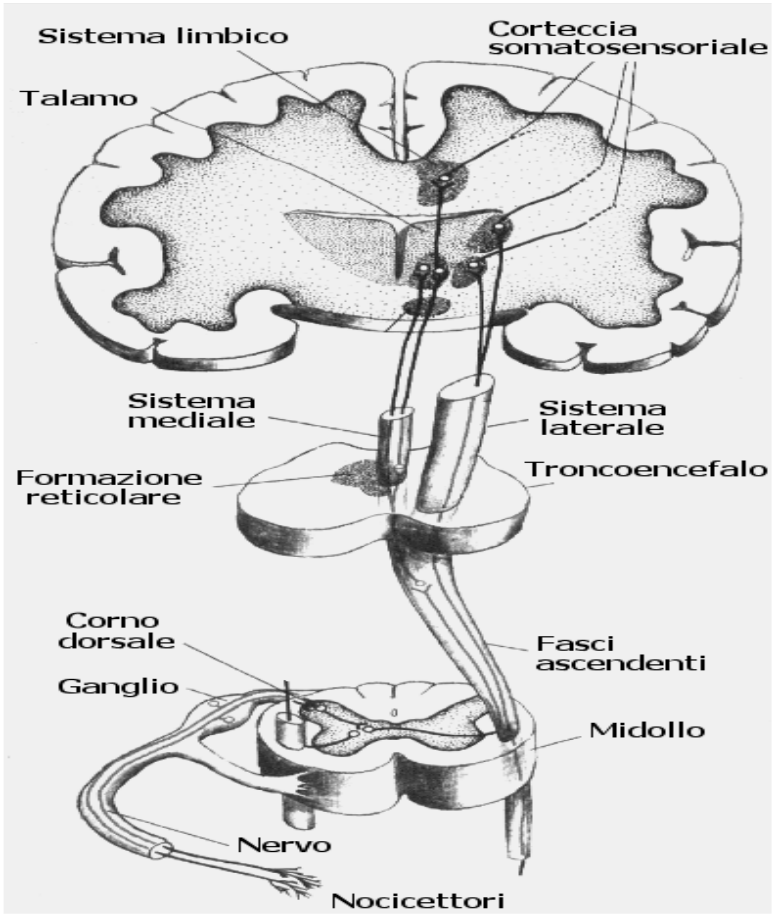
Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Antidepressants				
Amitriptyline, Clomipramine Imipramine Nortriptyline[b], Desipramine[b],	Monoamine reuptake inhibition; sodium channel blockade; anticholinergic effects	3.6 (3.0–4.4)	Somnolence, anticholinergic effects and weight gain	Cardiac disease, glaucoma, prostatic adenoma, seizure; high doses should be avoided in adults older than 65 years of age

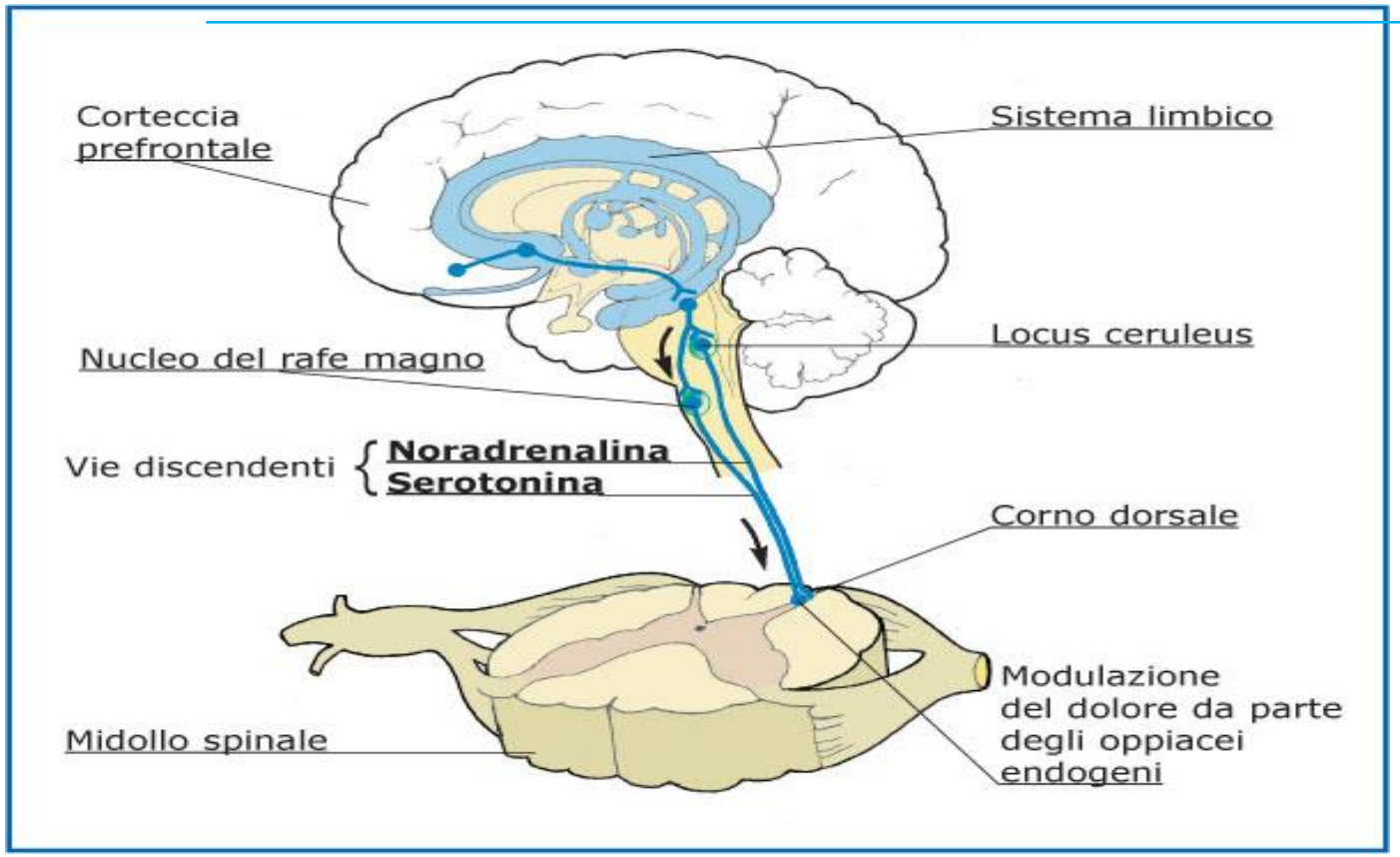
Azione analgesica conosciuta già dal 1960, si verifica a dosaggi più bassi rispetto all'azione antidepressiva

Sono risultati efficaci in diverse condizioni di dolore neuropatico; Neuropatie dolorose, neuropatia PH, Neuropatia diabetica dolorosa

Medication	Initial dosing	Effective dosing
Amitriptyline[10,102]	10–25 mg/d	50–150 mg/d
Nortriptyline[102,103]	10–25 mg/d	75–100 mg/d
Desipramine[102,103]	12.5–25 mg/d	Max dose: 150 mg/d
Imipramine[102]	50 mg/d	Max dose: 150 mg/d

Antidepressivi triciclici





- potenziamento vie inibitorie discendenti attraverso l'inibizione del reuptake di serotonina e noradrenalina
- inibizione sinaptica tra neurone di primo e secondo ordine mediante recettori alfa 2 adrenergici
- oppure tramite interneuroni con liberazione rispettivamente di GABA e oppioidi endogeni

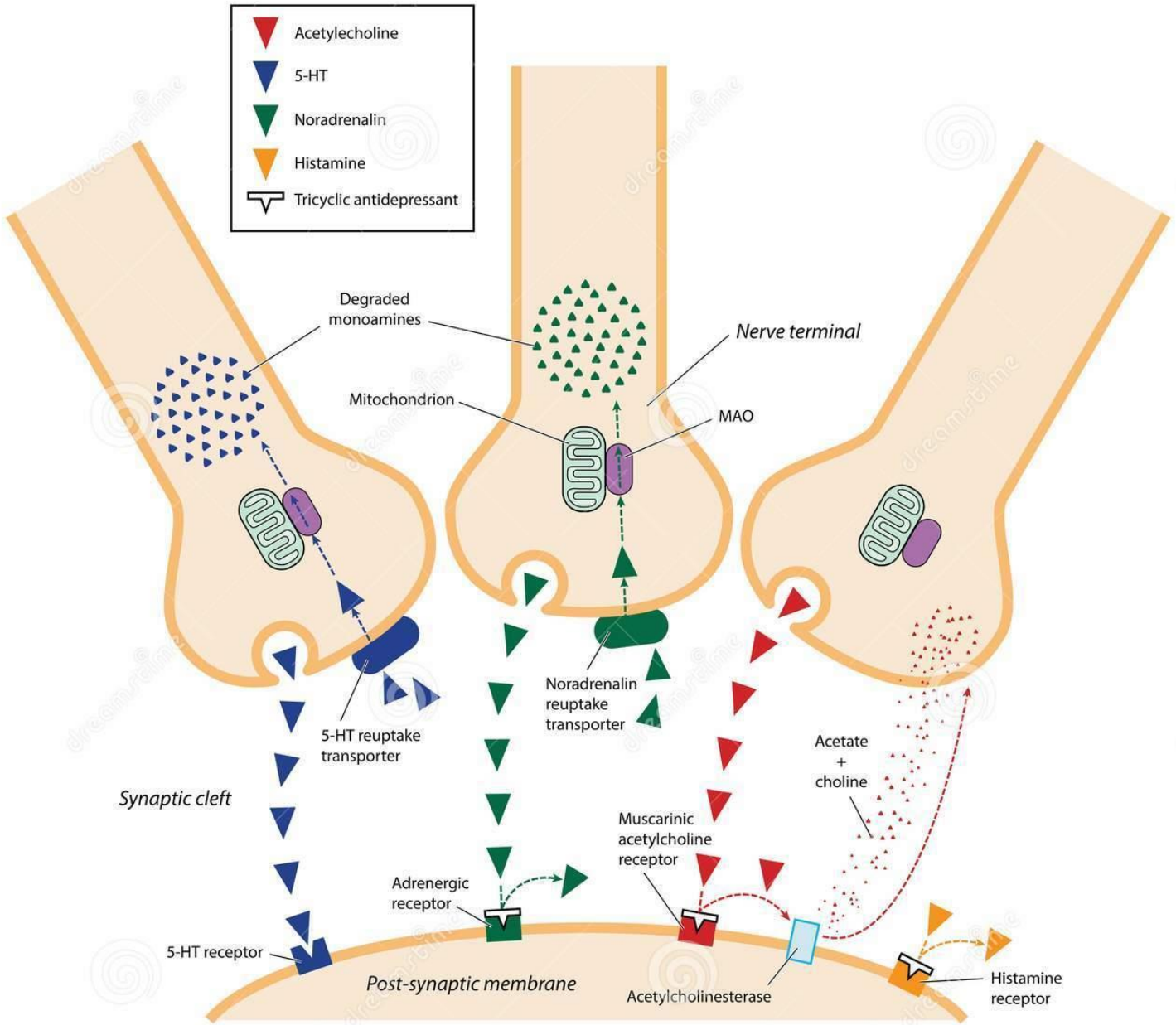
.

Antidepressivi triciclici

Dirty drugs per le multiple azioni.
L'efficacia clinica è anche legata a questa scarsa selettività.
Ad esempio l'amitriptilina ha anche un effetto anestetico locale per il blocco dei canali del sodio.

Numerosi effetti collaterali.
In particolare:
cardiotossicità , prolungamento QT, bocca secca, stipsi, ritenzione urinaria ipotensione ortostatica

Controndicazioni
Epilessia
Glaucoma
Ipertrofia prostatica
Aritmie cardiache



FARMACI DI PRIMA LINEA

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Duloxetine Venlafaxine	Serotonin and norepinephrine reuptake inhibition	6.4 (5.2–8.4)	Nausea, abdominal pain and constipation, hypertension at high dosages for venlafaxine	Hepatic disorder (duloxetine) Hypertension Cardiac disease Use of tramadol

potenziamento vie inibitorie discendenti attraverso l'inibizione del reuptake di serotonina e noradrenalina

Controindicati ancheç
Terapia con inibitori delle monoaminoossidasi o potenti inibitori CYP1A2 (fluvoxamina, ciprofloxacina)
Insufficienza renale grave (clearance della creatinina < 30 ml/min) – ipertensione non controllata

Medication	Initial dosing	Effective dosing
Venlafaxine[21,102]	37.5–75 mg/d	75–225 mg/d
Duloxetine[22,23,102]	20–30 mg/d	60–120 mg/d in divided dosing

FARMACI DI PRIMA LINEA

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Antiepileptics				
Gabapentin Gabapentin extended-release (ER)/enacarbil[b] Pregabalin	Act on Alpha2-Delta subunit of voltage-gated calcium channels, which decreases central sensitization	6.3 (5.0–8.4) for gabapentin 8.3 (6.2–13) for gabapentin ER/ enacarbil 7.7 (6.5–9.4) for pregabalin	Sedation, dizziness, peripheral edema and weight gain	Reduce dose in renal insufficiency

Il legame con la subunità alfa2-delta dei canali del calcio in diverse aree del SN spiega l'azione anticonvulsivante, ansiolitica e analgesica. Questo legame blocca il rilascio di neurotrasmettitori. Modulazione vie discendenti inibitorie

Non sono soggetti a metabolismo epatico ed in particolare al Citocromo P450, no interazioni farmacologiche
Molecole eliminate immodificate nella urine
Attenzione se il paziente assume ossicodone, lorazepam o etanolo

Gabapentin[40]	300 mg/d divided three times daily. Increase by 100–300 mg every 3–5 d	900–3,600 mg/d in divided dosing
Pregabalin[38,44–47]	150 mg/d, divided twice or three times daily	150–600 mg/d in divided dosing

Gabapentin:
assorbimento legato al sistema di trasporto aminoacidico Soggetto a saturazione ad alte dosi
Pregabalin:

- via alternativa per l'assorbimento
- maggiore affinità per alfa2-delta

FARMACI DI SECONDA LINEA

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Topical agents				
Lidocaine 5% plasters	Sodium channel blockade	NA	Local erythema, itching and rash	None
Capsaicin high concentration patches (8%)	Transient receptor potential vanilloid type 1 agonist (TRPV1)	10.6 (7.4–19)	Pain, erythema, itching; rare cases of high blood pressure (initial increase in pain)	No overall impairment of sensory evaluation after repeated applications, caution in progressive neuropathy
Opioids				
Tramadol	Mu receptor agonist; Monoamine reuptake inhibition	4.7 (3.6–6.7)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, use of antidepressant in elderly patients

Analgesici locali

Lidocaina: efficace nella neuropatia posterpetica e nell'allodinia

Capsaicina: desensibilizzazione TRPV1
- Efficace nella neuropatia dolorosa diabetica e non
- Dopo l'applicazione di cerotto 8% efficacia fino a 3 mesi
- Cicli ripetuti ogni 3 mesi mostrano la stessa efficacia del pregabalin in tutti i tipi di neuropatie dolorose

patch (8%) leads to reversible degeneration of nociceptive afferent fibers in the skin. Cutaneous innervation with nociceptive afferent fibers renormalizes in approximately 90 days (22).

Oppioide debole + SNRI

Tramadolo: azione oppioide debole associata a inibizione reuptake serotonina e norepinefrina

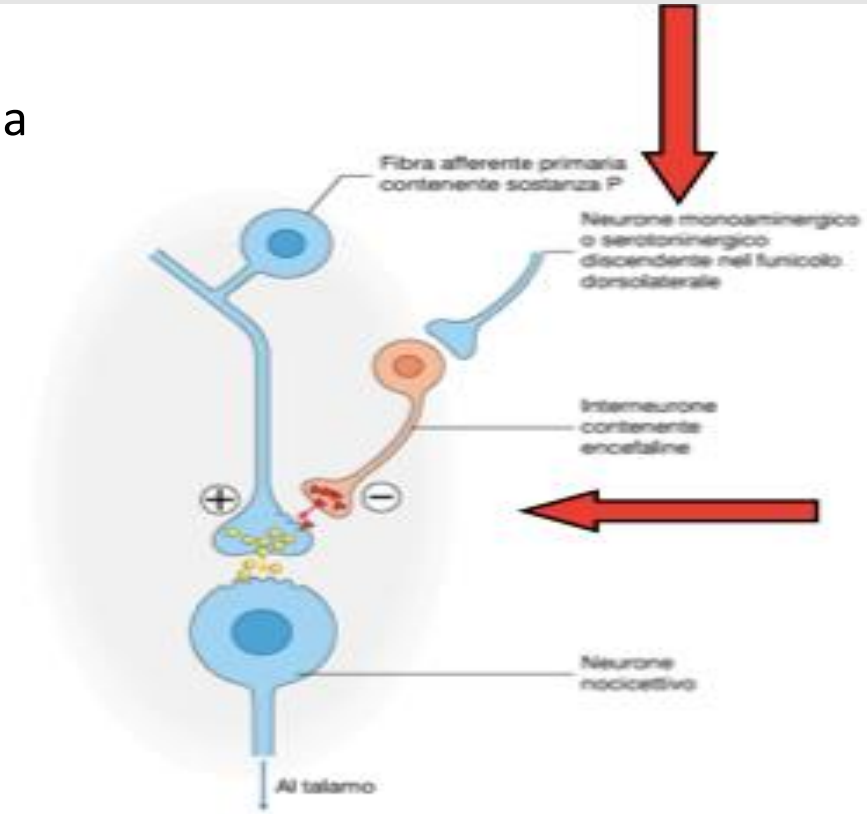
Rischio confusione e sonnolenza specie nell'anziano

FARMACI DI TERZA LINEA

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Strong opioids (e.g. morphine, oxycodone, methadone)	Mu receptor agonist; oxycodone may also cause kappa receptor antagonism	4.3 (3.4–5.8)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, risk of misuse on long-term use

- Quando c'è stata una scarsa risposta con i farmaci di I e II linea
- Nei pazienti neoplastici, quando si deve intervenire nel breve termine

- **Efficaci**
- **Rischio di dipendenza**

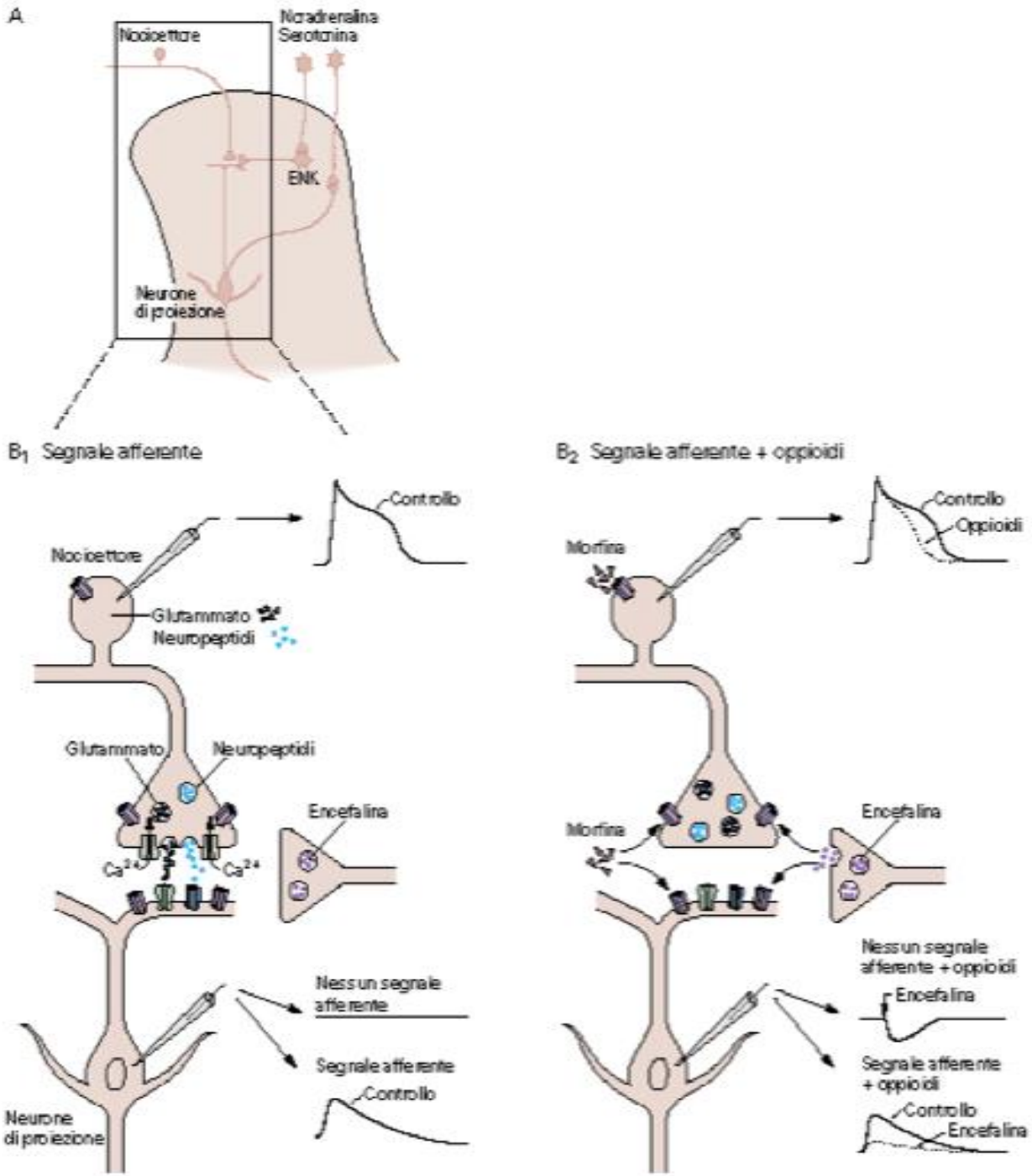


MECCANISMI D'AZIONE MOLECOLARE DEGLI OPPIODI

L'azione analgesica si esplica a livello del cervello, del tronco, del midollo spinale e del SNP attraverso i recettori mu, delta, kappa
I recettori sono accoppiati a proteine G, la cui attivazione determina ridotta produzione di c-AMP

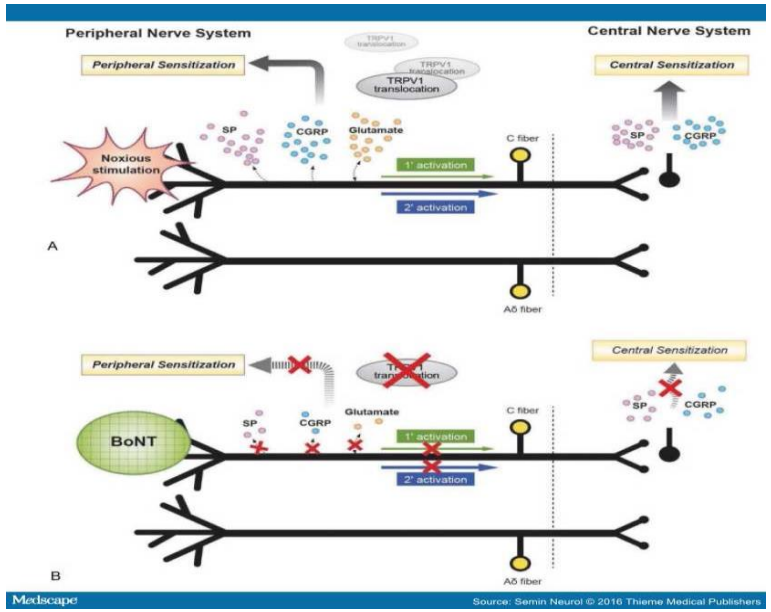
Inibizione presinaptica:
diminuito rilascio di glutammato e peptidi (sost.P) da inibizione canali Ca^{+} voltaggio dipendenti

Inibizione post-sinaptica:
aumento conduttanza al K



FARMACI DI TERZA LINEA

Drug	Mechanism of action	NNT for 50% pain relief and 95% confidence interval[a]	Adverse effects	Precautions, contraindications
Neurotoxins				
Botulinum toxin type A	Acetylcholine release inhibitor and neuromuscular blocking agent Potential effects on mechano-transduction and central effects in neuropathic pain	1.9 (1.5–2.4)[c]	Pain at injection site	Known hypersensitivity and infection of the painful area

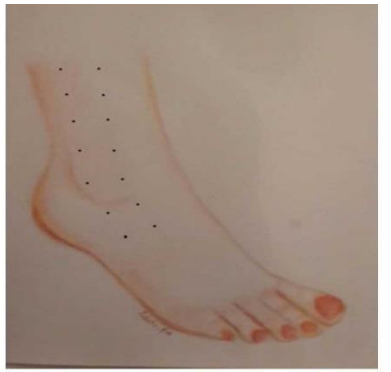


Safety and efficacy of repeated injections of botulinum toxin A in peripheral neuropathic pain (BOTNEP): a randomised, double-blind, placebo-controlled trial

Nadine Attal, Daniel C de Andrade, Frédéric Adam, Danièle Ranoux, Manoel J Teixeira, Ricardo Galhardoni, Irina Raicher, Nurcan Üçeyler, Claudia Sommer, Didier Bouhassira

Interpretation Two administrations of botulinum toxin A, each of which comprised several injections, have a sustained analgesic effect against peripheral neuropathic pain. Several factors, such as the presence of allodynia and a limited thermal deficit, may be useful in predicting treatment response and should be investigated further.

Efficace nel dolore neuropatico periferico, diabetico, posterpetico e nella nevralgia trigeminale



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FARMACI CON SCARSE EVIDENZE DI EFFICACIA

Cannabinoidi

Delta-9-tetraidrocannabinolo/cannabidiolo

Effetto su CB1 e CB2

Altri antiepilettici:

Topiramato, oxcarbazepina, carbamazepina, Valproato, lacosamide, levetiracetam

Received: 6 June 2018 | Accepted: 24 July 2018
DOI: 10.1002/ejp.1297

POSITION PAPER

WILEY EJP

European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management

Winfried Häuser[1,2] | David P. Finn[3] | Eija Kalso[4] | Nevenka Krcevski-Skvarc[5] | Hans-Georg Kress[6] | Bart Morlion[7] | Serge Perrot[8] | Michael Schäfer[9] | Chris Wells[10] | Silviu Brill[11]

The current status of evidence and of use of medical cannabis and of cannabis-based medicines for chronic pain in Europe is insufficient. A search in ClinicalTrials.gov as well as the contacts of the authors with pharmaceutical companies and colleagues demonstrated that new studies with cannabis-based medicines for chronic pain syndromes are designed and /or being conducted. The increase in the number of countries that have moved recently towards authorization of medical cannabis or cannabis-based medicines for chronic pain will also afford the opportunity for larger scale empirical and population-level studies which will further inform the evidence base. Therefore, we expect that the quantity and quality of evidence of as well as the clinical experience of physicians medical cannabis and cannabis-based medicines for chronic pain will substantially improve within the next three years. Therefore, we will update the position paper in 2021.

Sviluppo di nuovi farmaci

- Antagonisti Nav 1.7
- EMA 401 un nuovo antagonista dell'angiotensina II
- Antagonista TRPV1
- Antagonista NGF

Recupero di vecchi farmaci

Truini *et al. Molecular Pain* (2015) 11:14
DOI 10.1186/s12990-015-0009-2

MOLECULAR PAIN

RESEARCH Open Access

N-acetyl-cysteine, a drug that enhances the endogenous activation of group-II metabotropic glutamate receptors, inhibits nociceptive transmission in humans

Andrea Truini[1], Serena Piroso[1], Erica Pasquale[1], Serena Notartomaso[2], Giulia Di Stefano[1], Roberta Lattanzi[3], Giuseppe Battaglia[5], Ferdinando Nicoletti[3,4,5*] and Giorgio Cruccu[1]

L-acetil carnitina

ha dimostrato di indurre una up-regulation selettiva dei recettori sinaptici mGlu2, recettori con funzione di modulazione della trasmissione sinaptica eccitatoria

Chiechio S. et al. CNS Drugs 2007 *21 Suppl. 1: 31-38*

Journal of Pain Research
Dovepress
open access to scientific and medical research
Open Access Full Text Article
EXPERT OPINION

Combination treatment of neuropathic pain: Danish expert recommendations based on a Delphi process

This article was published in the following Dove Press journal:
Journal of Pain Research
26 June 2017

Table 2 Combination therapy with pregabalin or gabapentin

Pregabalin/gabapentin combined with:	CDC rating of scientific evidence	RCTs testing the combination	Clinical practice experience concerning combinations
TCAs	I + A	Gilron et al[10] and Holbech et al[11]	Combination well documented. Most with peripheral NeP. Useful combination for patients who do not tolerate either drug in larger doses, as well as sedative effect from TCA to improve sleep disturbance
SNRIs	I/II + B/C	Tesfaye et al[12] and Tannenberg et al[13]	Combination reasonably well documented. Used by some of the experts with good effect and fewer side effects than with TCA
SSRIs	III + C	None	Insufficient evidence available. SSRIs not relevant in the treatment of NeP
Opioids[a]	I + B	Gilron et al[16], Hanna et al[17] and Caraceni et al[18]	Good evidence to support combination therapy. Frequently used in daily clinical practice
Other antiepileptics[b] (Na+ channel blockers)	C	None	Insufficient evidence available. Combination could work in theory due to different mechanisms of action. Limited clinical experience
Cutaneous patches	I + A/C	Casale et al,[19] Meier et al[20] and Irving et al[21]	Mixed evidence and results for localized NeP. Patches add-on to oral therapy are used by some experts with good effect
Others	C	None	Insufficient evidence and clinical practice available

Notes: [a]Including synthetics. [b]Mainly sodium channel blockers, but also multiple mode of action drugs (valproic acid and topiramate).
Abbreviations: CDC, Centers for Disease Control and Prevention; NeP, neuropathic pain; RCTs, randomized controlled trials; SNRIs, serotonin-noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 4

Limitations of current clinical trials in neuropathic pain as outlined by the present meta-analysis and systematic review, and NeuPSIG recommendations for implementation of future clinical trials in neuropathic pain

Issues raised by current drug clinical trials in neuropathic pain	NeuPSIG recommendation for future trials in neuropathic pain
1/Patients population	
All RCTs have been conducted in adults	Conduct more studies in peadiatric population
Lack of validated diagnostic tools/algorithms for neuropathic pain	Use IASP diagnostic criteria for probable or definite neuropathic pain and validated screening tools to confirm diagnosis[1]
Classification of patients is generally based on aetiology	Classification should be based on sensory phenotypes rather than merely on aetiology[2]
2/ Characteristics of the trials	
Trial duration is 12 weeks or less in 81 % of the trials	Consider longer trial duration
High placebo response particularly in recent trials	Exclude patients with low pain intensity and high variability of pain at baseline[45]

Abbreviation: RCTs: randomized clinical trials

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

Ralf Baron, Matti Förster, Andreas Binder

Summary

Background Patients with neuropathic pain present with various pain-related sensory abnormalities. These sensory *Lancet Neurol* 2012;

Diversi trials con farmaci per il dolore neuropatico hanno dato risultati negativi nonostante i risultati incoraggianti da studi preclinici

Eterogenità del campione

Può aiutare la stratificazione dei pazienti in rapporto a patter sintomatologici che sottendono specifici meccanismi patogenetici?
Su 4200 pazienti con neuropatia diabetica, nevralgia posterpetica e radicolopatia dolorosa sono stati ottenuti con il PainDETECT
5 profili sensitivi
Al momento non ci sono studi su grosse popolazioni di pazienti stratificati in base al profilo sensitivo

The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: A randomised, double-blind, placebo-controlled phenotype-stratified study.
Demant, Dyveke T. et al *Pain.* 155(11):2263-2273, November 2014.

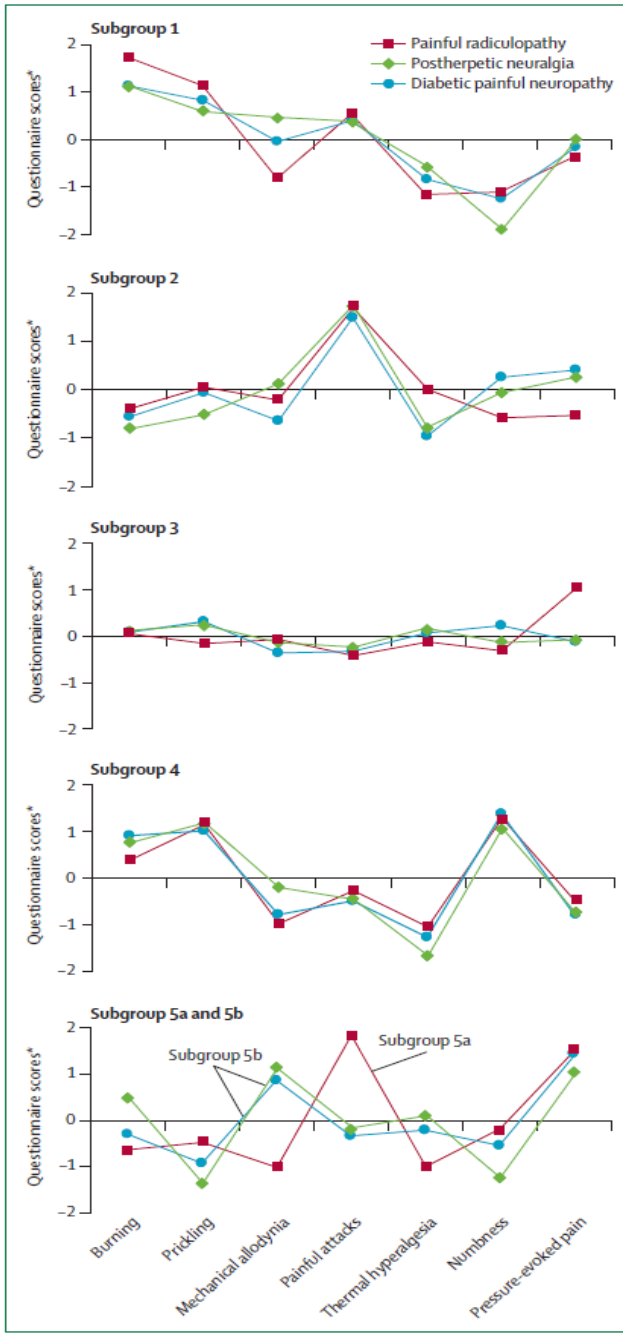


Figure: Subgroups of patients based on sensory symptoms assessed with PainDETECT

Irritable nociceptors, Peripheral and central sensitisation

Ectopic activity in primary Nociceptive neurons, Increased expression of voltage gated Na channels

Patients with difficulties In describing the different symptoms

Severe deafferentation
Central sensitisation

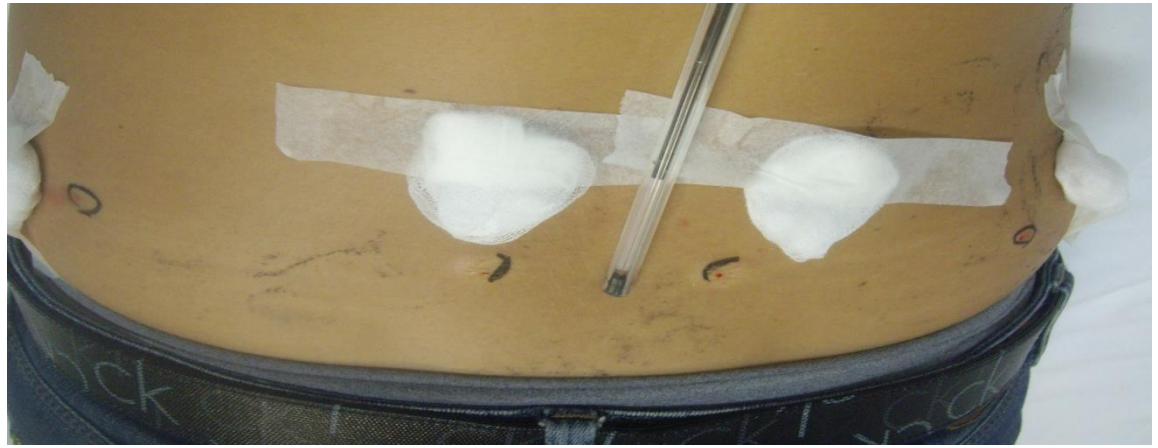
Pain attacks
Ectopic discarges in the Nociceptive neurons after slight compression of inflamed dorsal root

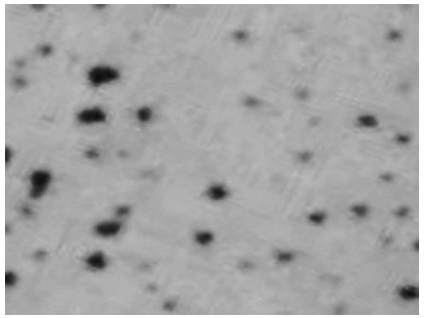
A patient with postherpethic burning pain

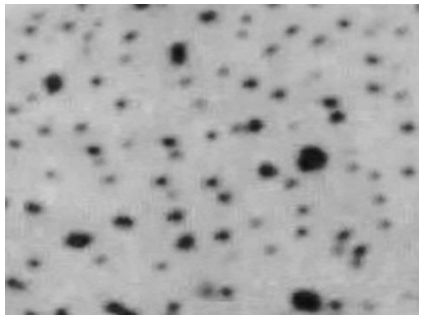
❖ CASE REPORT *

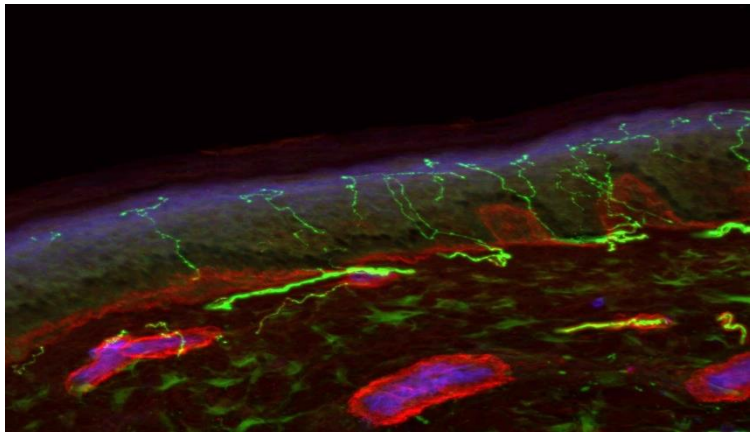
32 year old woman

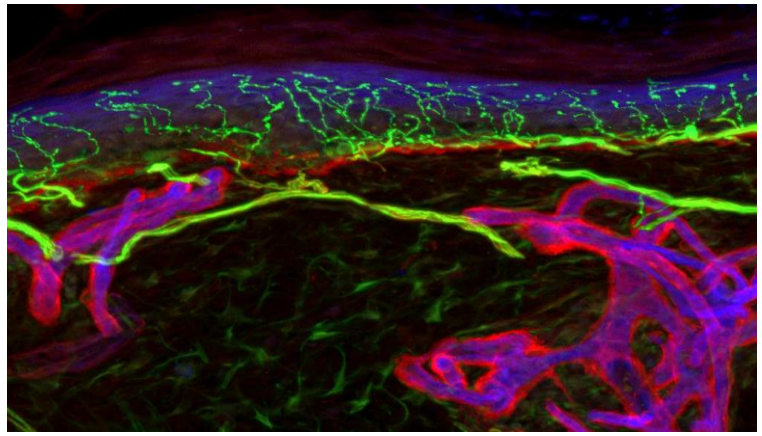
- ✓ Postherpethic burning pain in right lumbar region
- ✓ Severe mechanical dynamic allodynia
- ✓ QST hyperalgesia and lower sensory thresholds
- ✓ No response to drugs











* Unpublished data

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Medicine 2016

CONTINUING MEDICAL EDUCATION

The Pharmacological Therapy of Chronic Neuropathic Pain

Andreas Binder, Ralf Baron

The fundamentals of treatment

Pain should be treated at once if it impairs the patient's functioning in everyday life. The treatment options should be discussed clearly with the patient to prevent excessively high expectations and possible disappointment *(Box 2)*. Drugs can lessen neuropathic pain by 30–50% (6). Complete freedom from pain often cannot be achieved. For all types of drug, 20–40% of patients either experience less than 30% pain reduction (so-called "non-responders") or have intolerable side effects (6). The choice of drug is independent of the etiology of neuropathic pain (12, 15–18), but some drugs have not been tested or approved for pain of some etiologies.

To improve compliance, patients should also be informed about the following before the treatment is begun:

Realistic treatment goals

- 30–50% pain reduction
- Better sleep
- Better quality of life
- Maintenance of social activity
- Recovery and maintenance of ability to work

Treatment options

Drug treatment can be combined at any time with non-pharmacological treatments, and indeed should be if indicated. These treatments include physiotherapy, psychotherapy, and transcutaneous electrical nerve stimulation (TENS).

Doctors put drugs
of which they know *little*
into bodies
of which they know *less*
for diseases
of which they know *nothing at all*

VOLTAIRE 1694-1778