Clinica e terapia del dolore neuropatico

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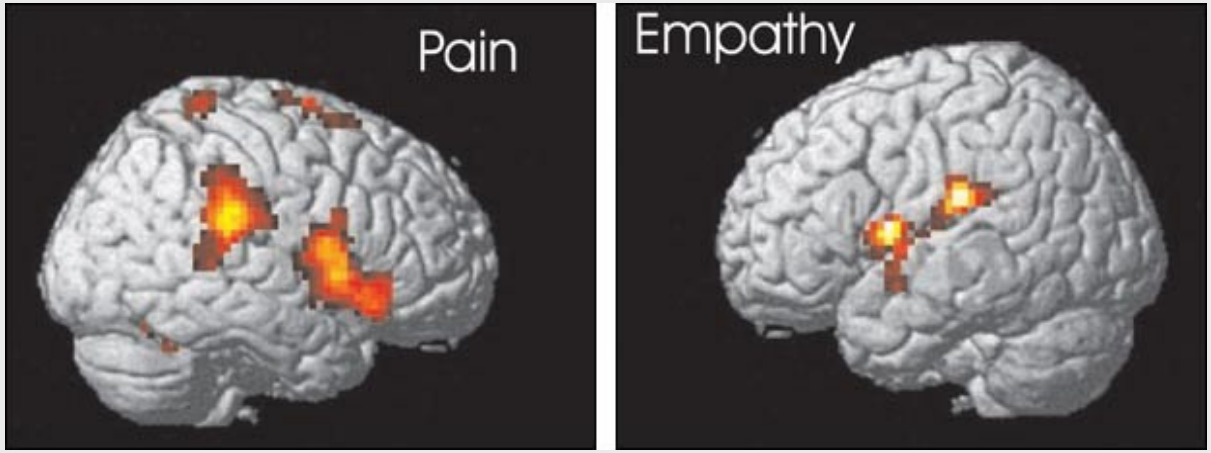
Definizione di dolore

Esperienza sensoriale ed emozionale spiacevole, associata ad un danno tissutale o potenziale, o descritto in tali termini

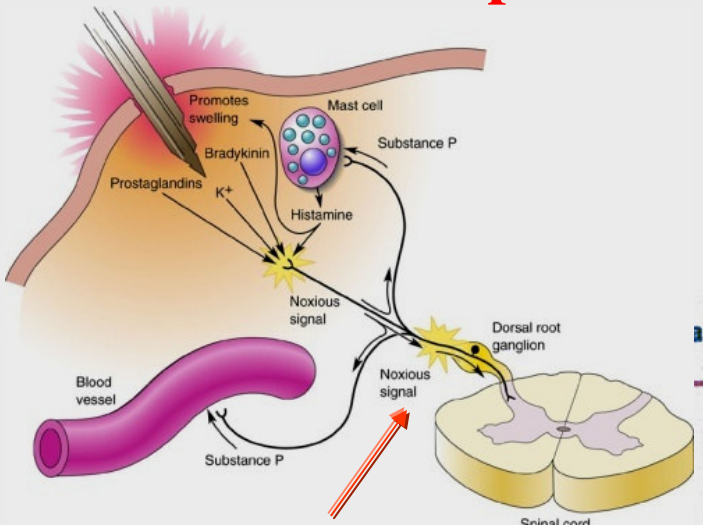
(IASP)

Il dolore consiste di quattro componenti:

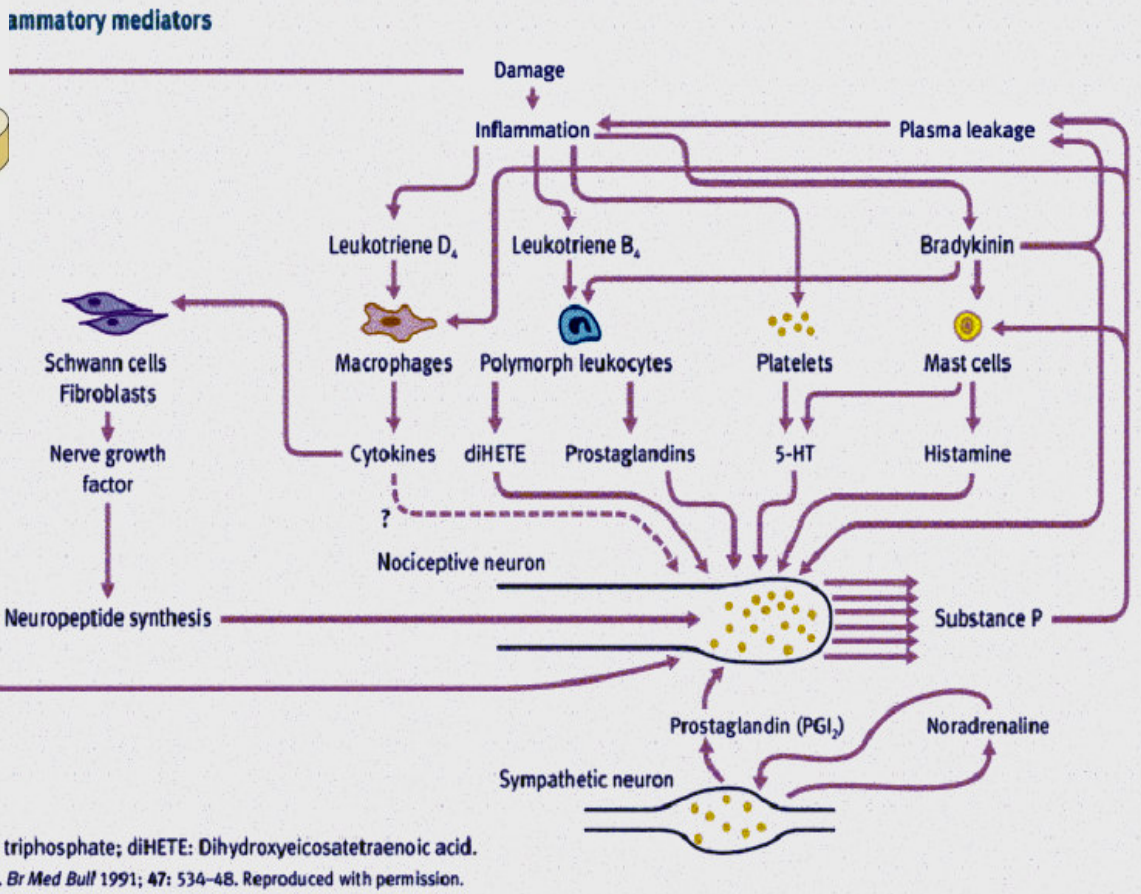
1) nocicezione
2) sensazione
3) affettività
4) comportamento



Nociceptive mechanism



C Fibers



ATP: Adenosine triphosphate; diHETE: Dihydroxyeicosatetraenoic acid.

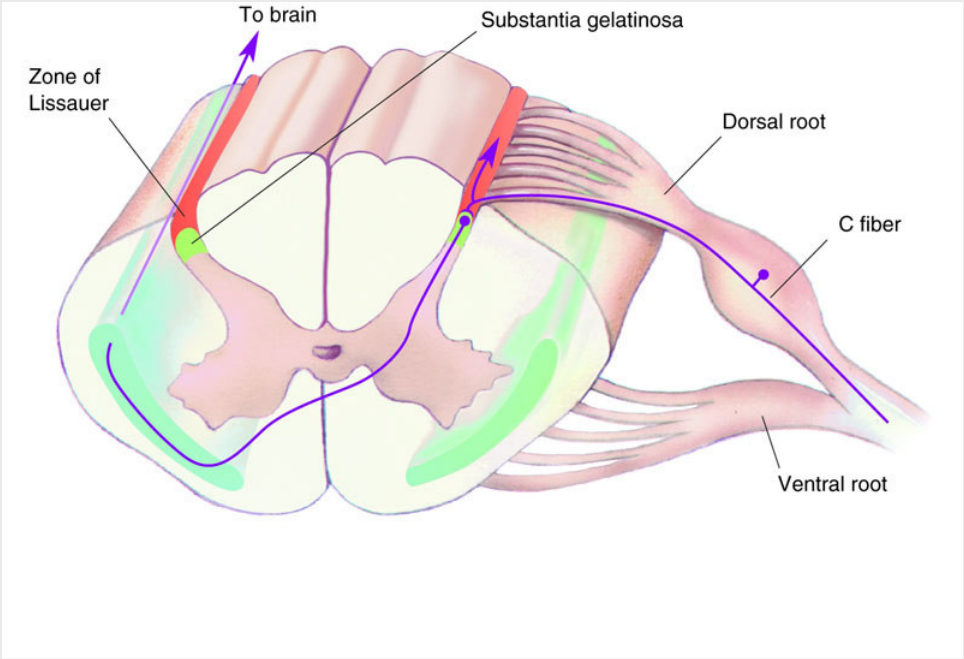
Source: Wells JCD. *Br Med Bull* 1991; 47: 534–48. Reproduced with permission.

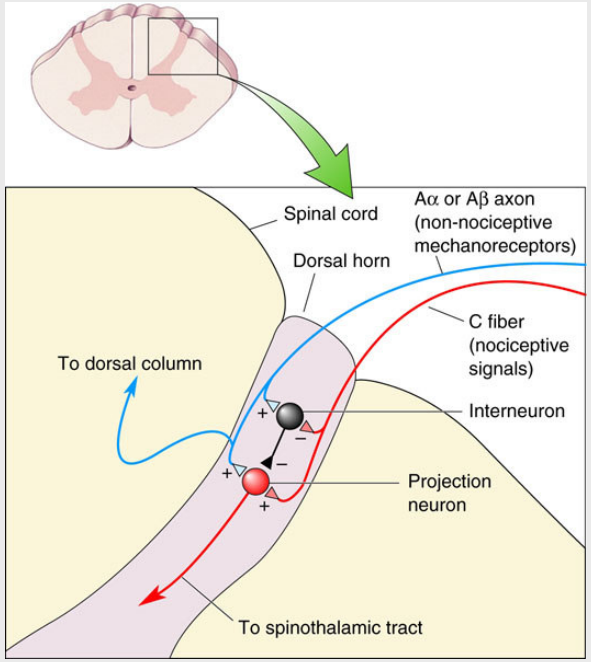
Dorsal Horn Transmission

Competition for opportunities to stimulate ascending pathways:

1. *encephalin-producing descending fibres* from the brain stem interact with both pre-synaptic and post-synaptic cells to ***inhibit transmission***.

2. the "*pain gate*" by Melzack and Wall: incoming signals in the A beta fibres of a peripheral nerve ***can alter sensitivity*** of the post-synaptic cells to painful stimuli arriving in C and A delta fibres.





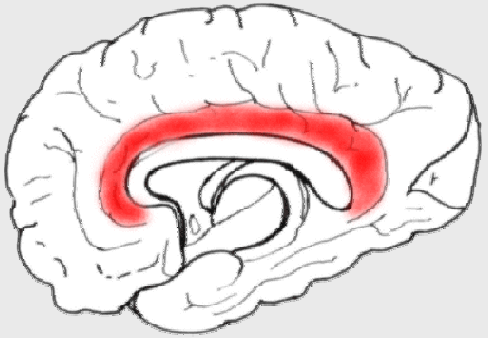
Descending Pain Modulating Pathways

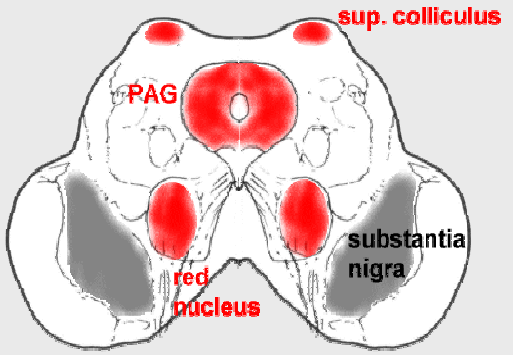
These arise in the

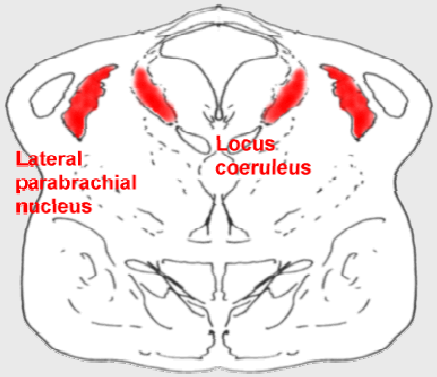
- cerebral cortex and pass to the
  nucleus gracilis and cuneatus
  reticular formation, thalamus

- periaqueductal grey (PAG) matter and
  pass to the dorsal horn directly
  raphe nuclei of medulla, and then to dorsal horn

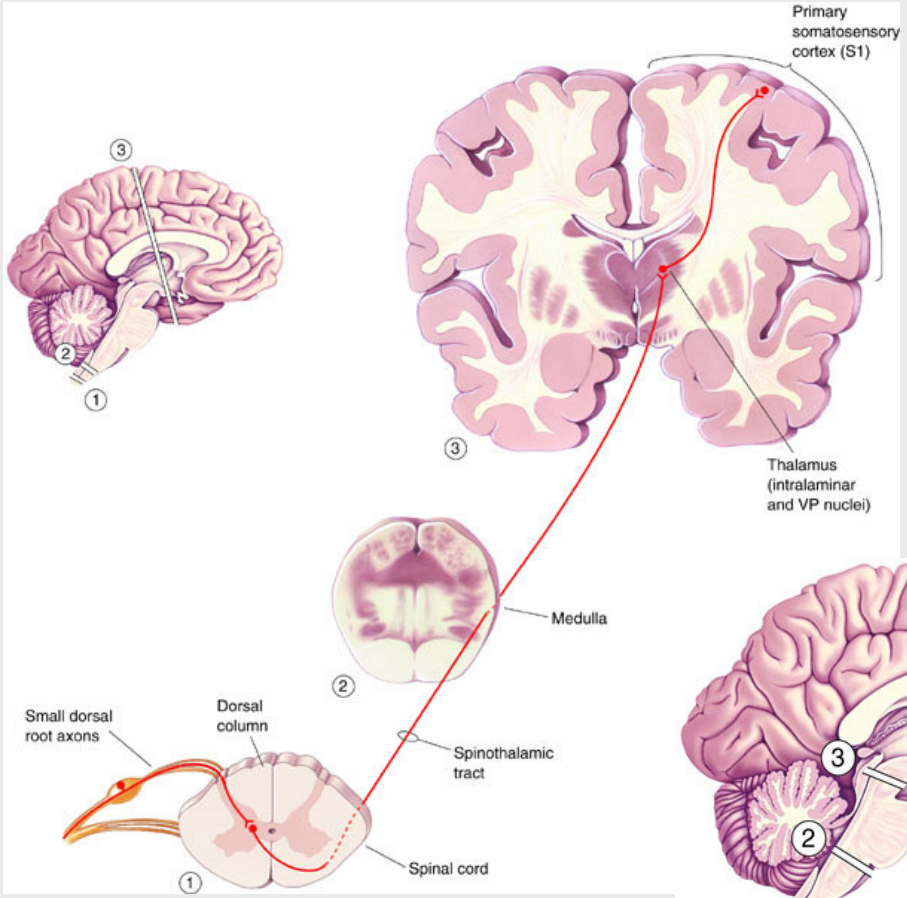
- locus ceruleus and pass to the
  dorsal horn of spinal cord





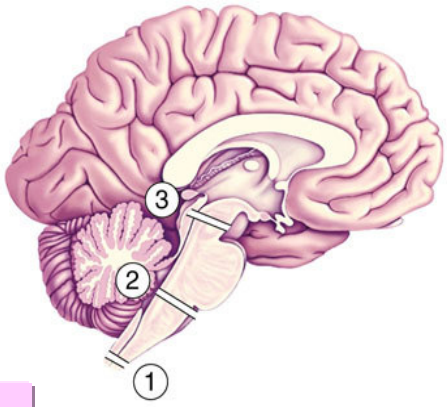


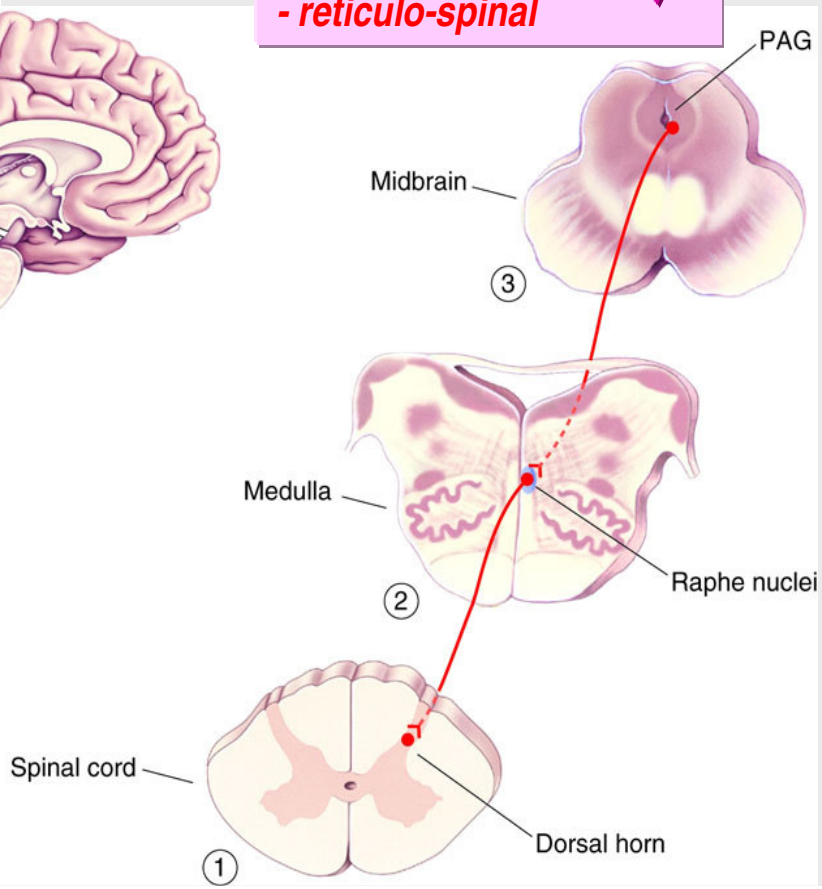
Ascending and Descending Pain Connections



- *Spino-thalamic pathway*
- *Spino-reticular pathway*
- *Spino parabrachial pathway*
- *Spino-hypothalamic pathway*
- *Dorsal column pathway* Visceral

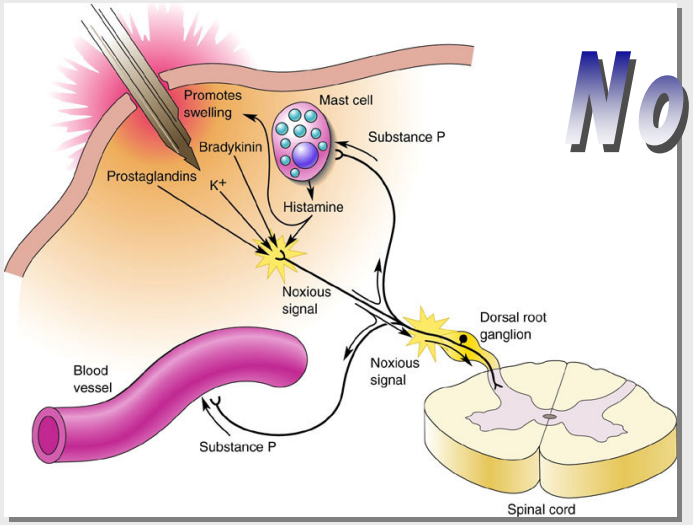
- *Cortex*
- *PAG*
- *raphe nuclei*
- *locus ceruleus*
- *parabrachial*
- *reticulo-spinal*

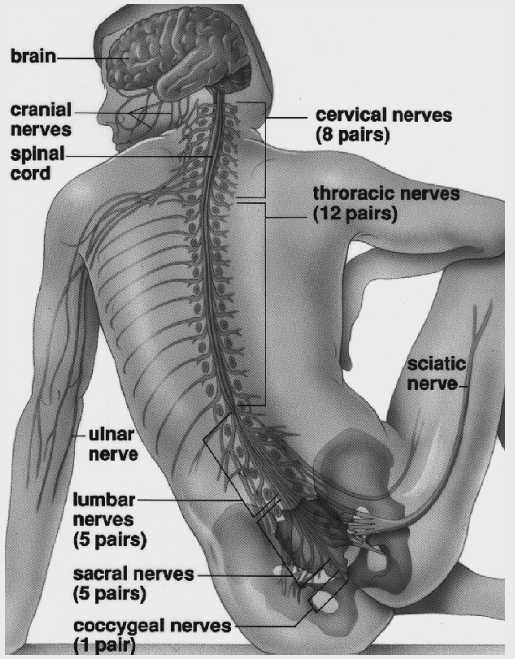




….The reign of pain is mainly in the brain. But there is no one centre "in control". Rather we see that pain can be all-pervasive

Nociceptive pain





Neuropathic pain

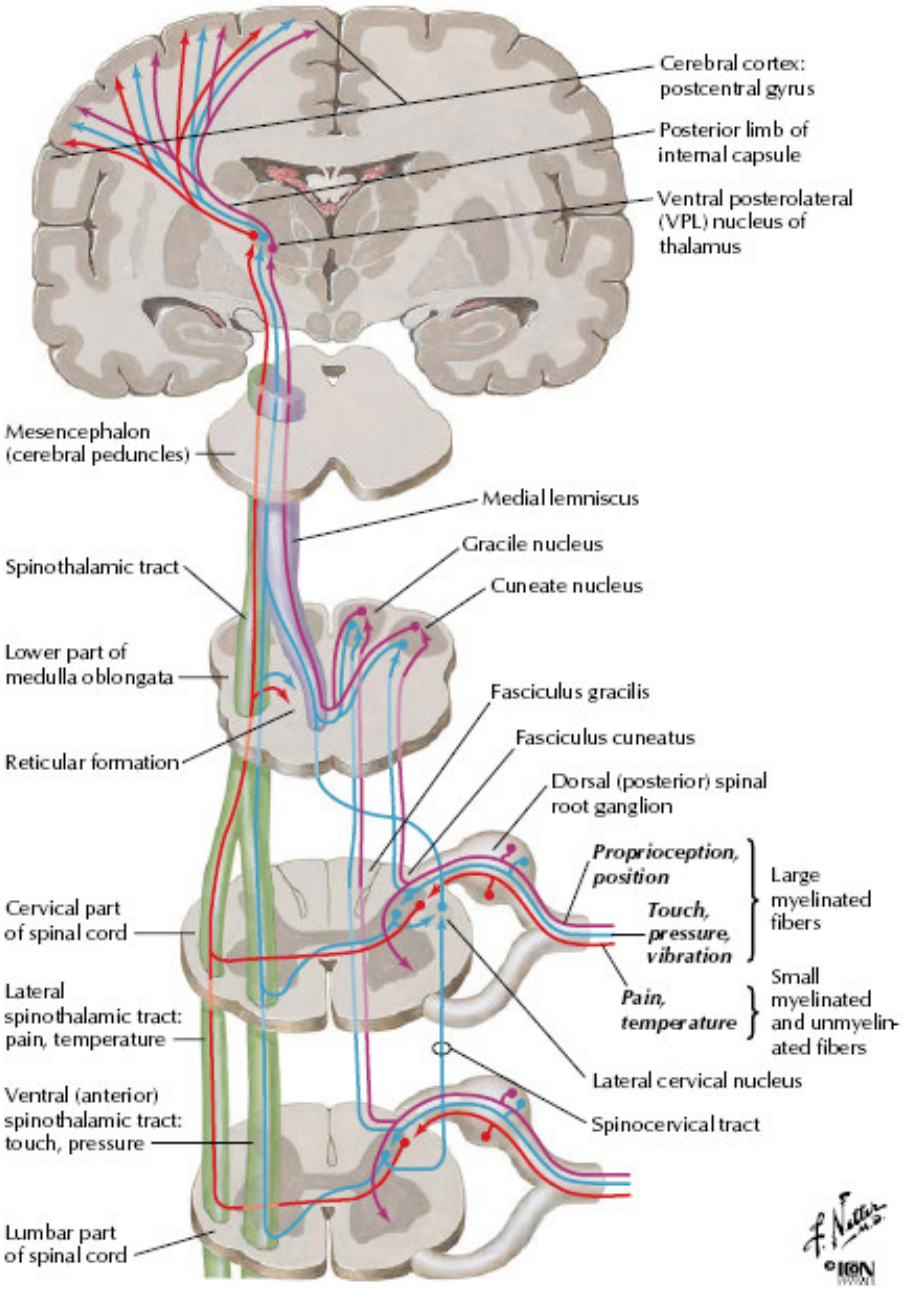
Neuropathic pain

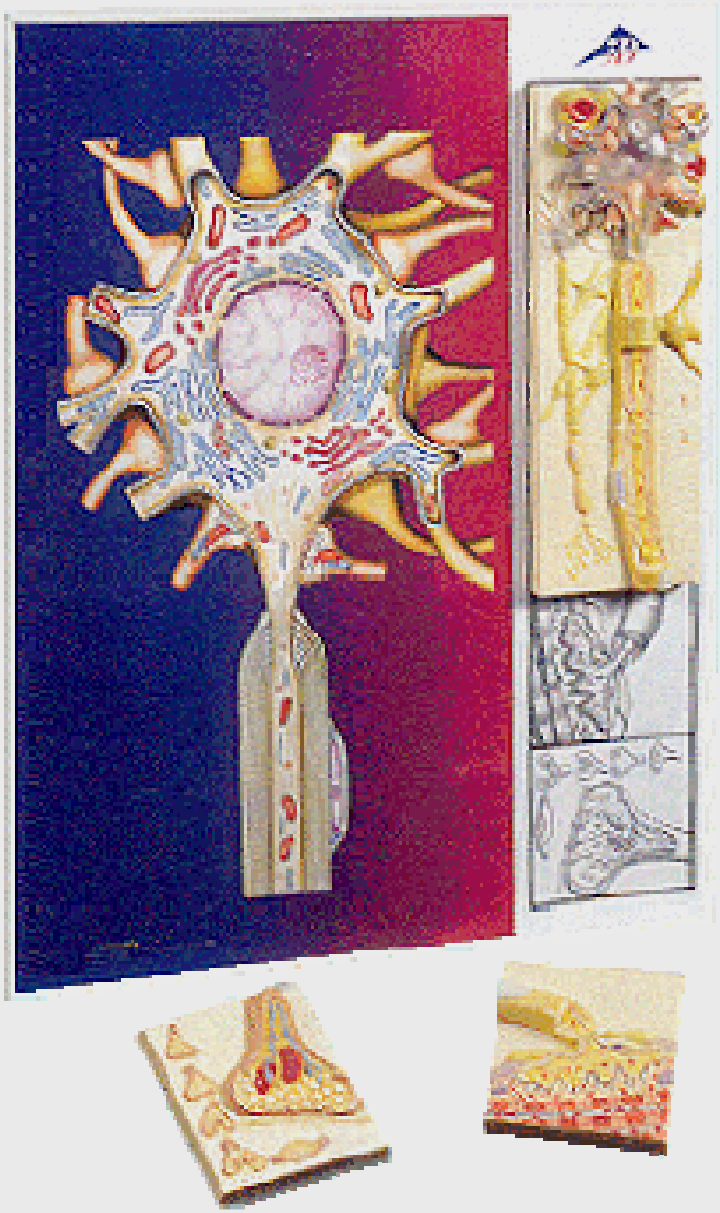
‘pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system (CNS)’

International Association for the Study of Pain (IASP), 1994

‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system’

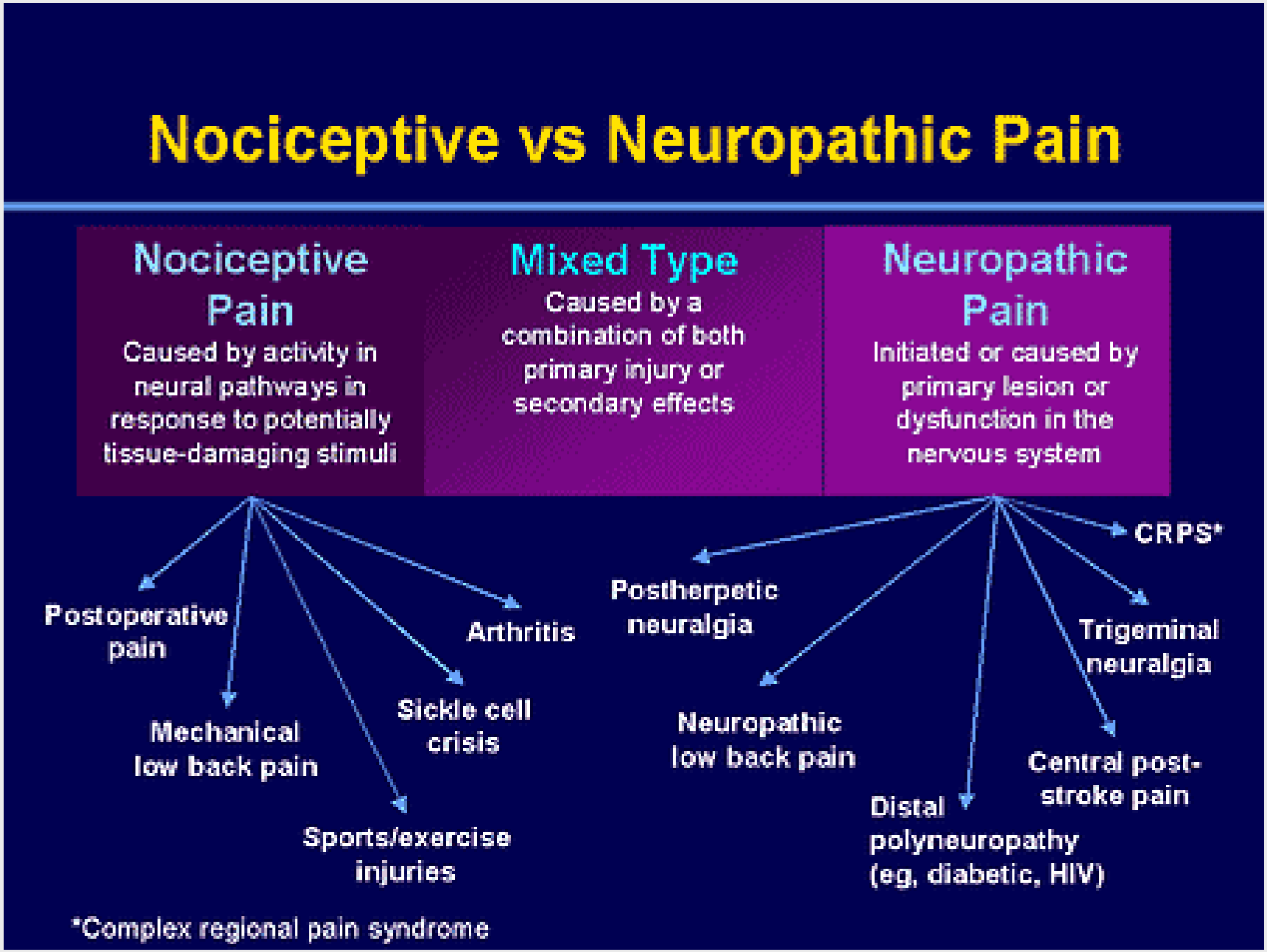
Treede et al, 2008


Cerebral cortex: postcentral gyrus
Posterior limb of internal capsule
Ventral posterolateral (VPL) nucleus of thalamus
Mesencephalon (cerebral peduncles)
Medial lemniscus
Gracile nucleus
Spinothalamic tract
Cuneate nucleus
Lower part of medulla oblongata
Fasciculus gracilis
Fasciculus cuneatus
Reticular formation
Dorsal (posterior) spinal root ganglion
Proprioception, position
Touch, pressure, vibration
Large myelinated fibers
Cervical part of spinal cord
Lateral spinothalamic tract: pain, temperature
Pain, temperature
Small myelinated and unmyelinated fibers
Lateral cervical nucleus
Ventral (anterior) spinothalamic tract: touch, pressure
Spinocervical tract
Lumbar part of spinal cord



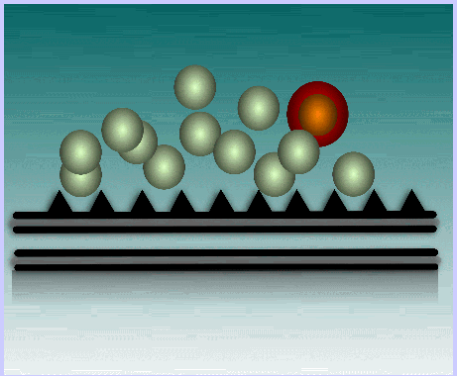
“Neuropathic Pain is not a symptom nor a single disease but represents a syndrome, a constellation of specific symptoms and signs with multiple potential underlying aetiologies

Nociceptive vs Neuropathic Pain



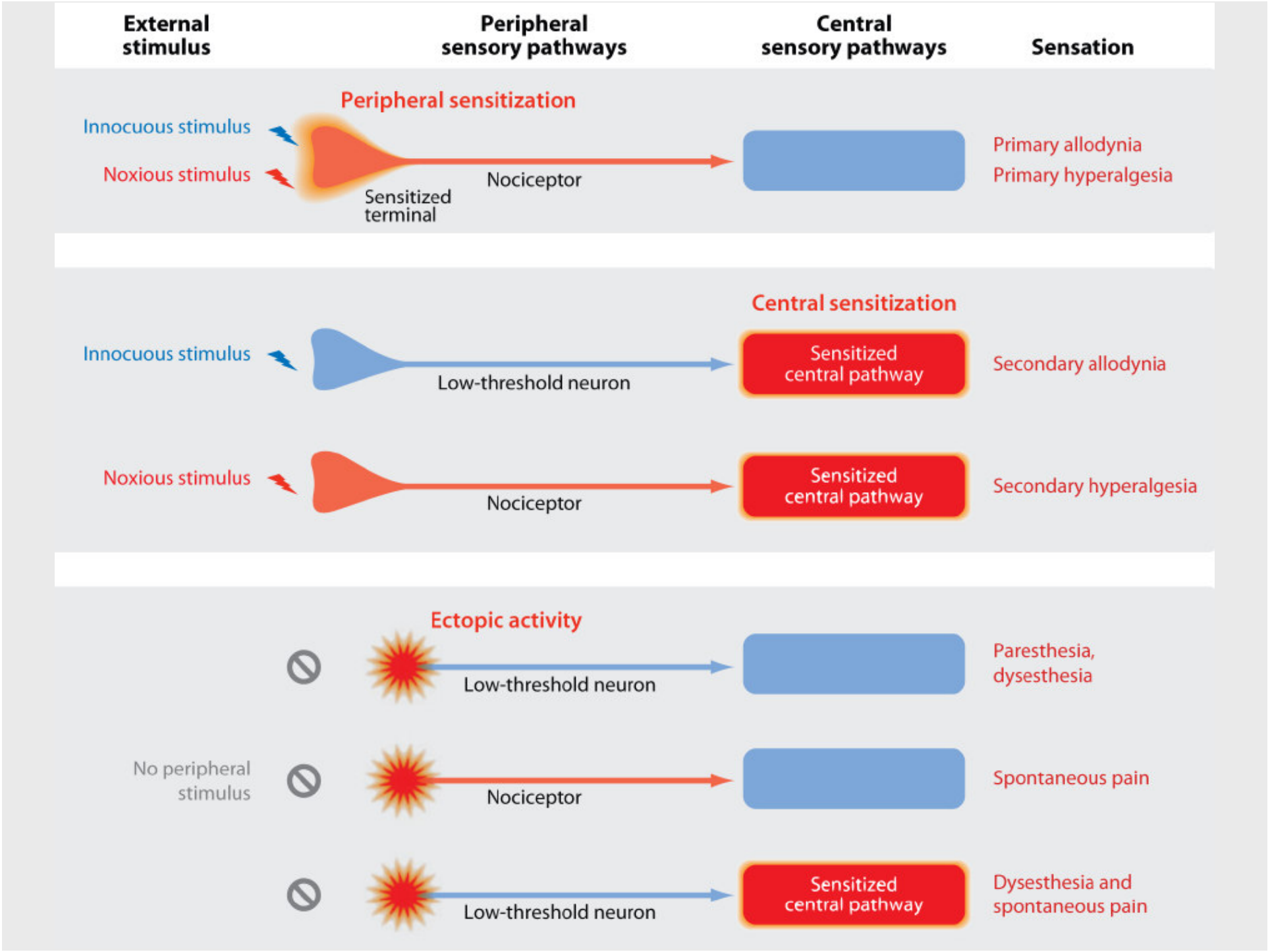
Central nervous system **neuropathic mechanism** may include:

- spontaneous neuronal activity,
- abnormal temporal integration of stimuli,
- abnormal excitability of sensory transmission neurons,
- decreased inhibition within the spino-thalamic tract



The supraspinal **neuropathic changes** associated with chronic pain have been described in terms of:

- corticalization of chronic pain,
- a memory like state,
- thalamic plasticity
- cortical hyperexcitability.


External stimulus
Peripheral sensory pathways
Central sensory pathways
Sensation
Peripheral sensitization
Innocuous stimulus
Noxious stimulus
Sensitized terminal
Nociceptor
Primary allodynia
Primary hyperalgesia
Central sensitization
Innocuous stimulus
Low-threshold neuron
Sensitized central pathway
Secondary allodynia
Noxious stimulus
Nociceptor
Sensitized central pathway
Secondary hyperalgesia
Ectopic activity
Low-threshold neuron
Paresthesia, dysesthesia
No peripheral stimulus
Nociceptor
Spontaneous pain
Low-threshold neuron
Sensitized central pathway
Dysesthesia and spontaneous pain

Assessing the Patient Who Has Pain

- Onset and duration
- Location/distribution
- Quality
- Intensity
- Aggravating/relieving factors
- Associated features or secondary signs/symptoms
- Associated factors
  - mood/emotional distress
  - functional activities
- Treatment response

Clinical Assessment: Neurologic History

- Symptoms
- Onset
- Etiologic factors
  - diabetes mellitus (undiagnosed)
  - alcohol
  - vitamin deficiencies (B_{12}, thiamine, etc)
  - hereditary
  - neurotoxicity (environmental, iatrogenic)
  - trauma/structural lesions (herniated nucleus pulposus, carpal tunnel syndrome)

Clinical Assessment: Psychosocial History

- Current psychiatric symptoms
- History of addictive disease
- Change in social function
  - work
  - family and relationships
  - recreation
- Medical-legal status

Diagnostic Studies and Limitations

Studies

- Blood studies
- X-ray, CT, MRI
- Electromyography (EMG)
- Nerve conduction velocity (NCV)
- Quantitative sensory testing (QST)
- Epidermal skin biopsy

Limitations of EMG/NCV

- Insensitive in acute injury
- Normal result does not rule out neuropathic pain
- Cannot assess function of small-fiber nerves involved in most neuropathic pain

Microneurography

Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. McGraw-Hill Companies; 2000.

A. History: character and distribution of the pain according with neuropathic criteria, and relevant lesion or disease in the nervous system probably responsible for the pain

B. Clinical examination: presence of negative (loss of function) and positive (hyperalgesia and/or allodynia) sensory signs, for one or more sensory modalities

C. Further diagnostic tests: to document a specific underlying neurological disease (e.g. imaging of the brain in a patient with suspected CPSP) or confirm a sensory lesion within the pain distribution (e.g. skin biopsy to document small fibre neuropathy)

- **Possible NP** (fulfilling step A above)

- **Probable NP** (fulfilling A with supporting evidence for either lesion/disease **or** pain distribution according to B or C)

- **Definite NP** (fulfilling A with supporting evidence for both lesion/disease **and** pain distribution according to B and C)

Questionari e scale per lo screening

- McGill Pain Questionnaire (MPQ)

- Leeds Assessment of Neuropathic Symptoms
- and Signs (LANSS)

- Neuropathic Pain Questionnaire (NPQ)

- **Douleur Neuropathique en 4 questions (DN4)**

- PainDETECT

- ID Pain

- Standardized evaluation of pain (StEP)

Douleur Neuropathique en 4 questions (DN4)

Il **DN4** è stato testato in 160 pazienti con dolore sia neuropatico che nocicettivo e consta di 7 items collegati ai sintomi e 3 collegati all'esame clinico.

E' facilmente compilabile e un punteggio totale di almeno 4 su 10 suggerisce un dolore neuropatico.

Il DN4 mostra una **sensibilità del 83% e una specificità del 90%** quando è comparato con la diagnosi clinica.

I 7 items che descrivono la sensibilità possono essere utilizzati come un questionario che il paziente autocompila, con risultati analoghi.

Lo strumento è stato sviluppato e validato in Francia e tradotto in altre lingue.

QUESTIONARIO DN 4

Compilare il questionario scegliendo una risposta per ciascuno dei punti proposti nelle domande riportate sotto:

INTERVISTA AL PAZIENTE

Domanda 1:
il dolore ha una o più delle seguenti caratteristiche?

- BRUCIANTE/URENTE SI NO
- SENSAZIONE DI FREDDO DOLOROSO SI NO
- SCOSSE ELETTRICHE SI NO

Domanda 2:
il dolore è associato ad uno o più dei seguenti sintomi nell'area del dolore stesso?

- FORMICOLIO SI NO
- PUNTURE DI SPILLO SI NO
- INTORPIDIMENTO SI NO
- PRURITO SI NO

ESAME DEL PAZIENTE

Domanda 3:
il dolore è localizzato nella stessa area dove l'esame fisico può rilevare una o piu' delle seguenti caratteristiche ?

- IPOESTESIA AL TATTO SI NO
- IPOESTESIA ALLA PUNTURA SI NO

Domanda 4:
nell'area dolente il dolore può essere causato o peggiorato dallo

- SFIORAMENTO DELLA PELLE SI NO

PUNTEGGIO DEL PAZIENTE >/= 4 **/10**

Il punteggio si calcola attribuendo un punto ad ogni risposta positiva.

Score di valutazione gravità

- SF-MPQ 2
- Neuropathic Pain Scale (NPS
- Pain Quality Assessment Scale (PQAS)
- **Neuropathic Pain Symptom Inventory (NPSI)**

Neuropathic Pain Symptom Inventory (NPSI).

Neuropathic Pain Symptom Inventory

Severity of the spontaneous pain

Q1. Does your pain feel like burning?

Q2.Does your pain feel like squeezing?

Q3.Does your pain feel like pressure?

Q4. During the past 24 h, your spontaneous pain has been present: permanently / 8 to 12 h/4 to 7 h/1 to 3 h/<1 h

Severity of the painful attacks

Q5.Does your pain feel like electric shocks?

Q6. Does your pain feel like stabbing?

Q7. In the past 24 h how many of these pain attacks have you had? >20/11 to 20/6 to 10/1 to 5 none

Severity of your provoked pains

Q8. Is your pain provoked or increased by brushing on the painful area?

Q9. Is your pain provoked or increased by pressure on the painful area?

Q10. Is your pain provoked or increased by contact with something cold on the painful area?

Severity of abnormal sensations

Q11. Do you fee l pins and needles?

Q12. Do you feel tingling?

Quantitative sensory testing (QST)

- QST is a psychophysiological measure of perception in response to external stimuli of controlled intensity

- Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude

- Most QST studies are still dedicated to the assessment of sensory small fibre function only

- QST is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components (grade A)

Pain-related reflexes

A beta - mediated trigeminal reflexes (early R1 blink reflex and early SP1 masseter inhibitory reflex) are efficient tools to reveal symptomatic forms of trigeminal neuralgia (specificity of 94% and sensitivity of 87%)

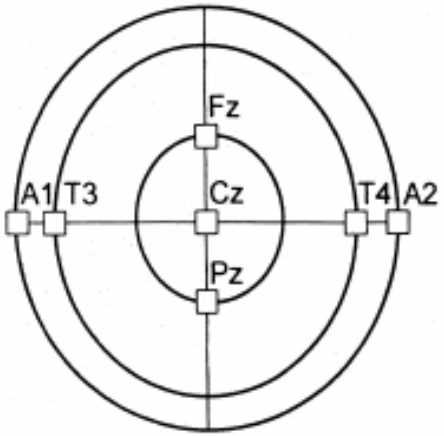
Pain-related evoked potentials

Laser-evoked potentials (LEPs) are the easiest and most reliable methods for assessing function of nociceptive pathways (A delta and C fibre pathways)

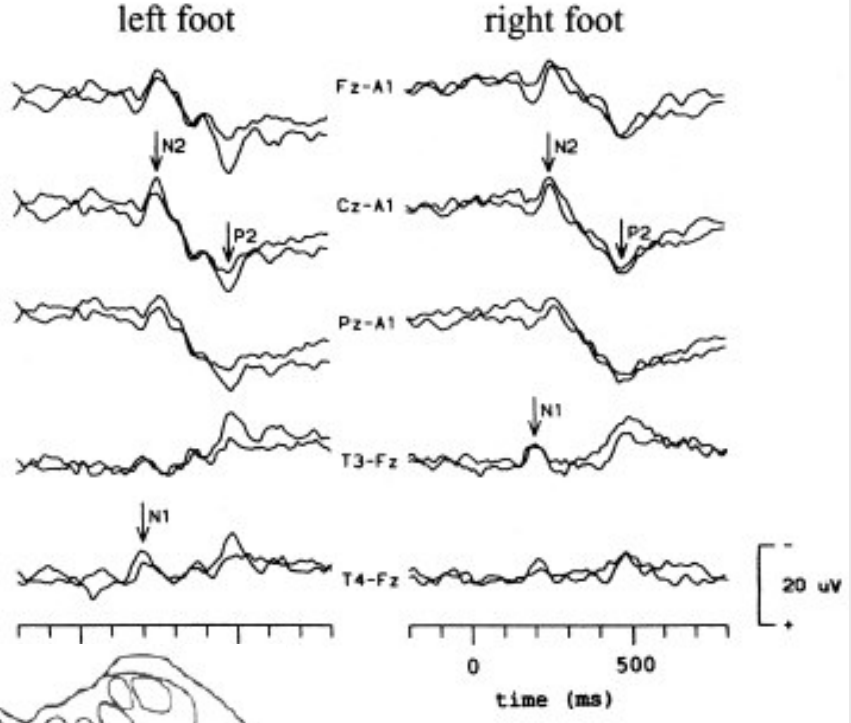
A: Laser evoked potentials: methods

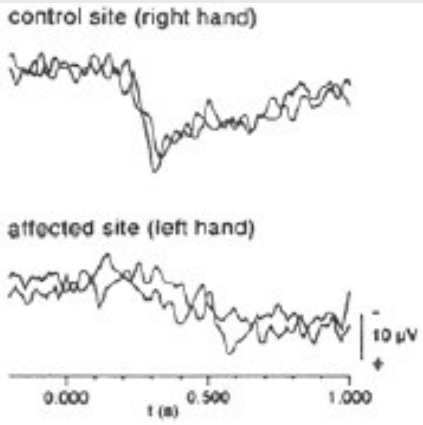
Stimuli:
painful heat pulses generated by an infrared laser (wavelength 2010 nm),
3 ms duration, 5 mm diameter,
2 runs of 20 stimuli (540 mJ energy)

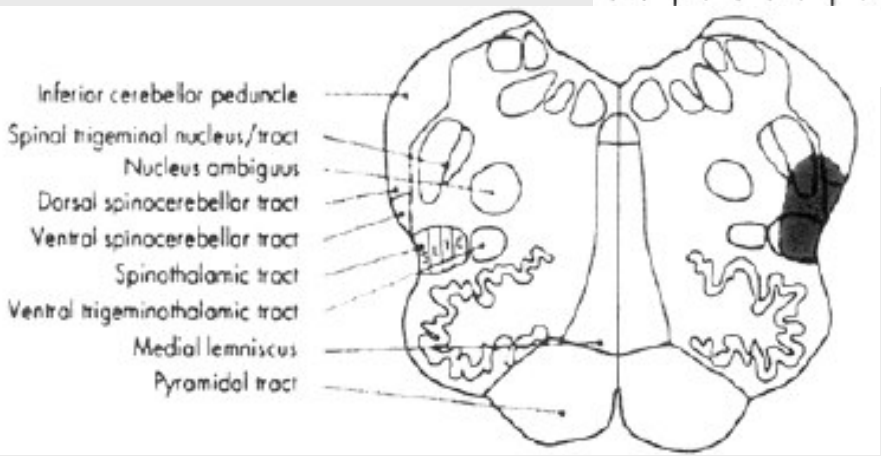
Recording:
0.2-70 Hz bandpass,
200 Hz sampling rate,
Fz, Cz, Pz vs. earlobes, T3, T4 vs. Fz

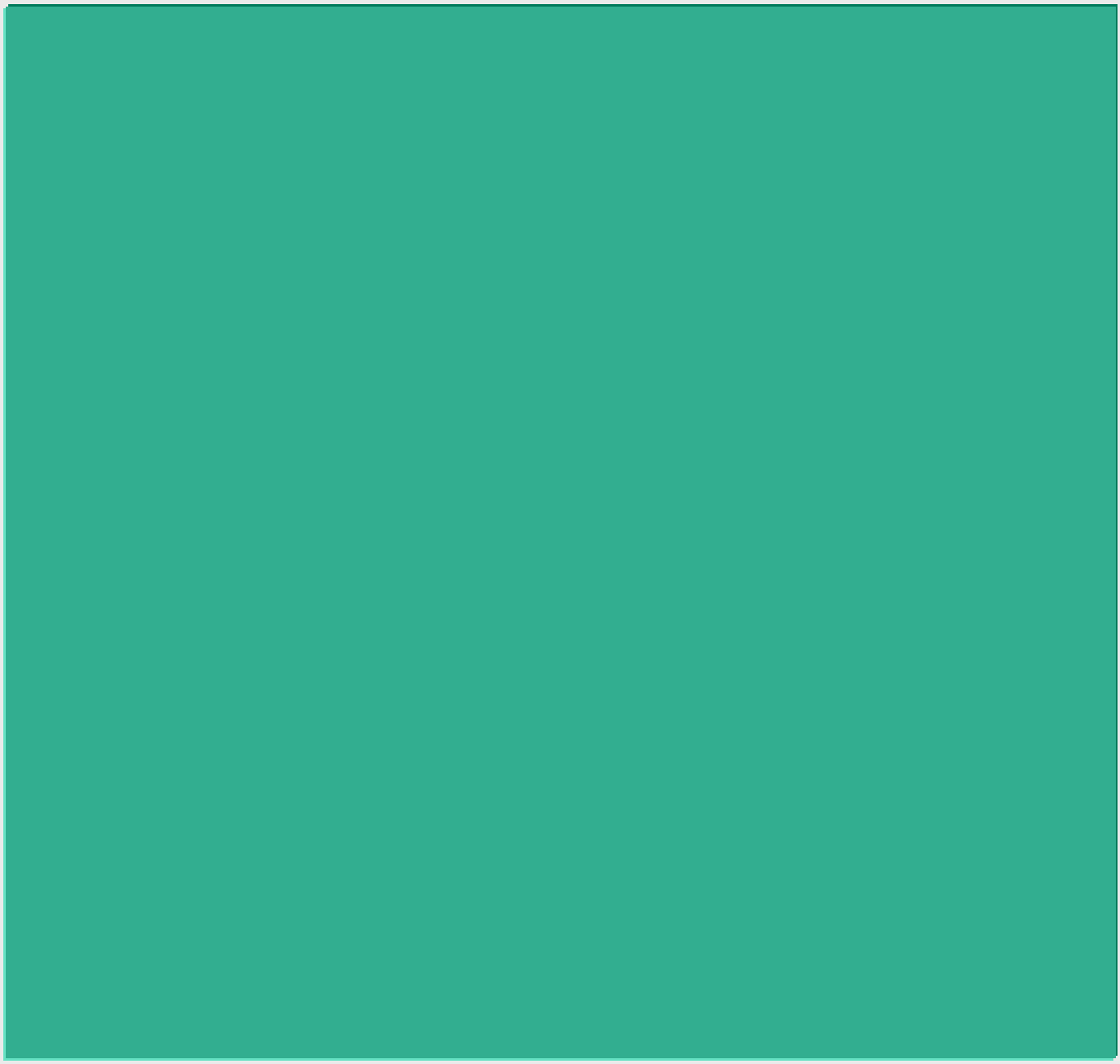


B: Laser evoked potentials: normal subject



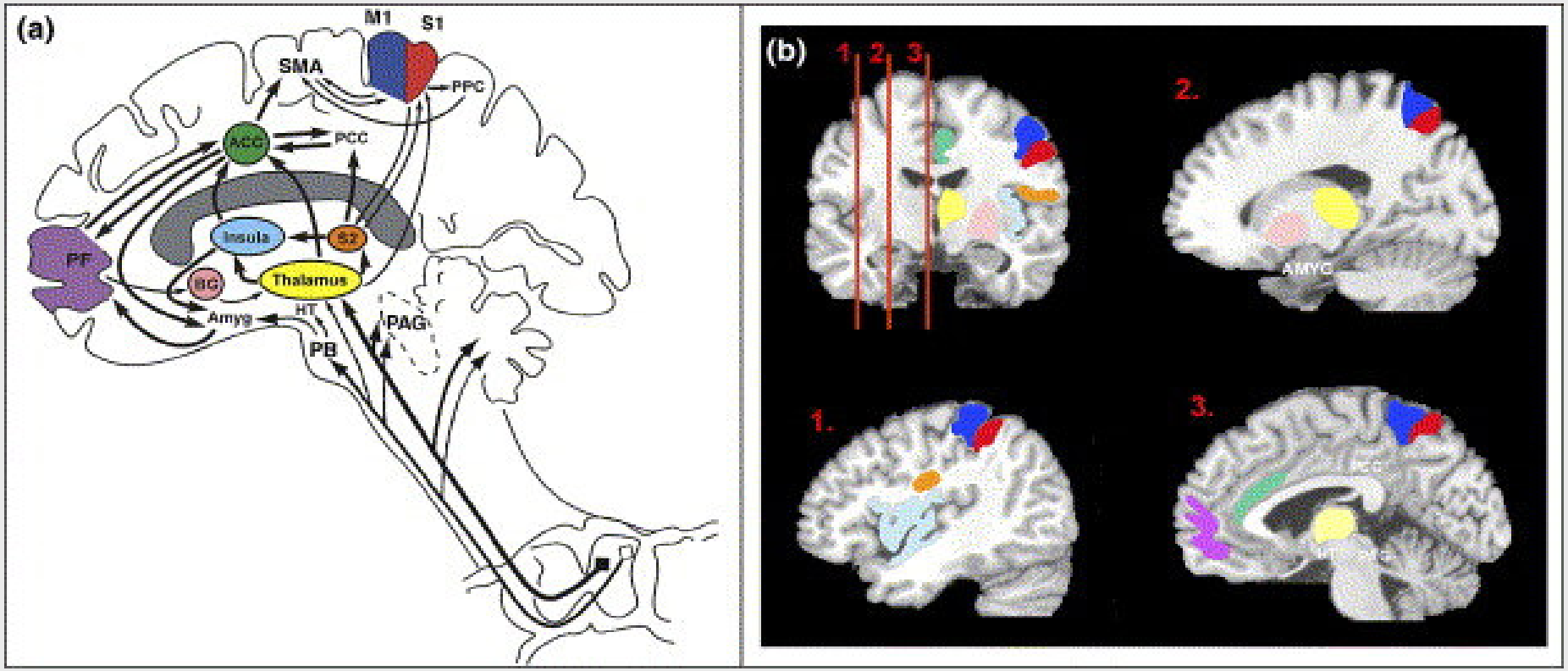




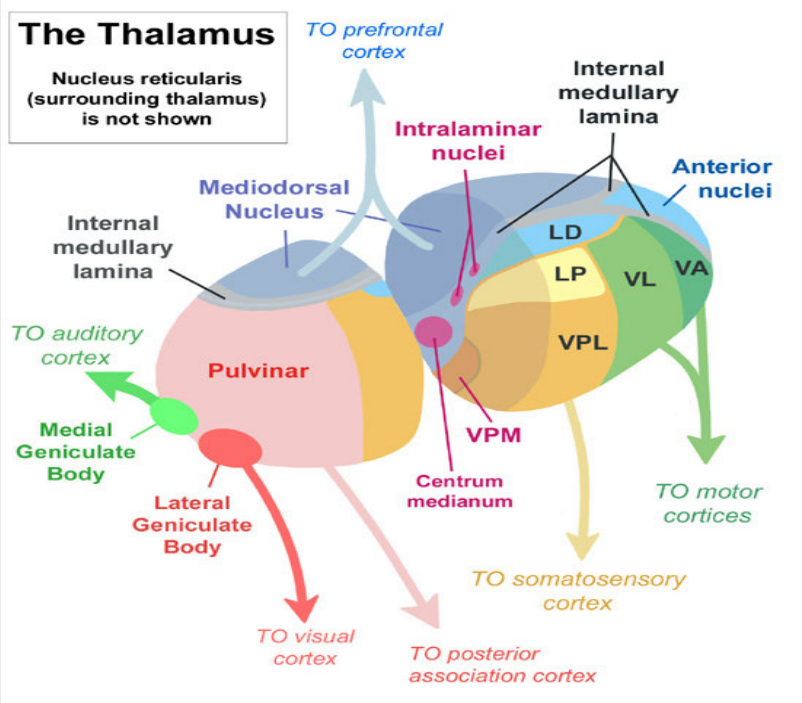


Functional neuroimaging

Positron Emission Tomography (**PET**), functional Magnetic Resonance Imaging (**fMRI**) and measure with different methods Cerebral Blood Flow (**rCBF**)



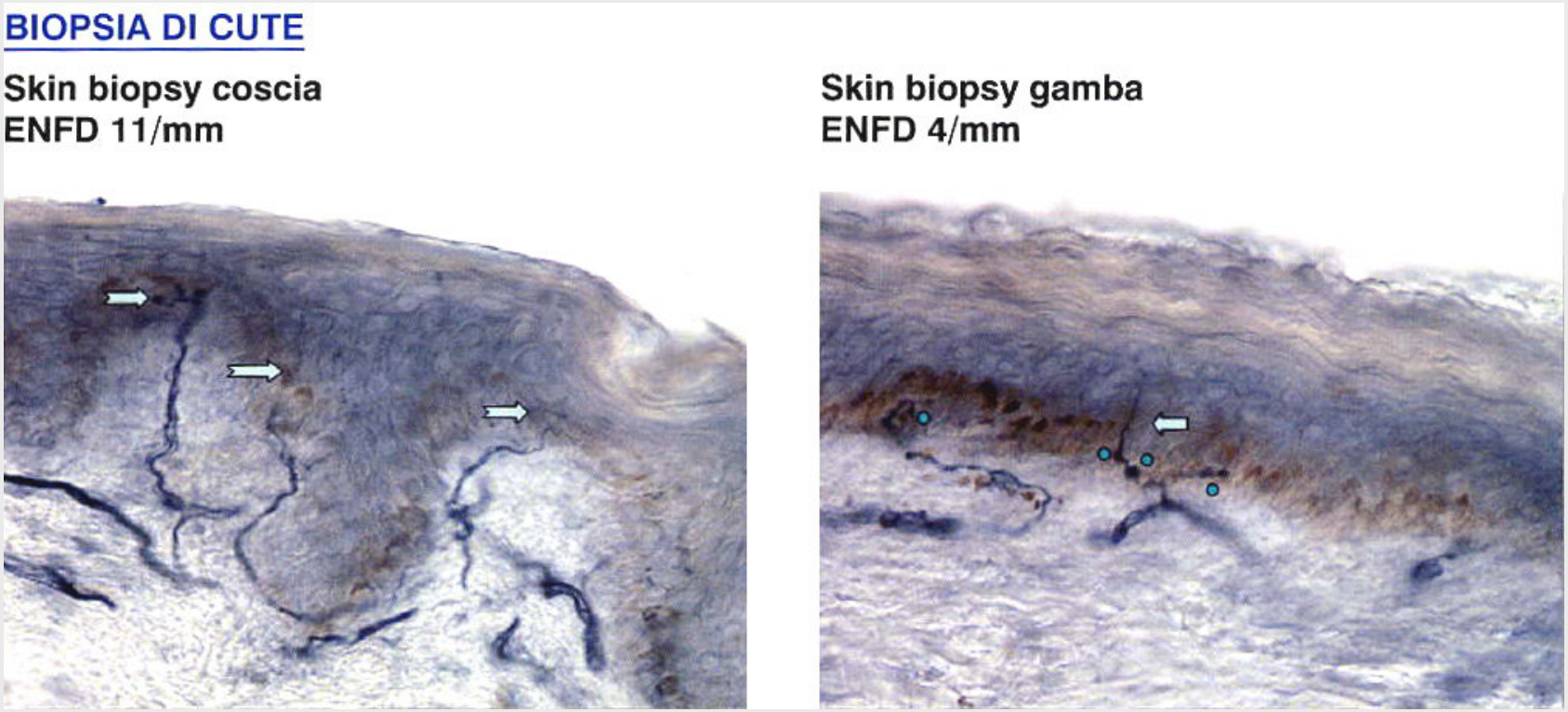
Network of **somatosensory**, **limbic** and **associative structures** receiving parallel inputs from multiple nociceptive pathways. The **strong affective-motivational** character of pain is exemplified by the participation of regions such as the **cingulate**



Chronic pain is associated with **decreased perfusion of the thalamus** (along with other structures), while **experimental/acute pain** in healthy subjects is associated with **increased perfusion of the thalamus**.

Skin biopsy

• Immunostaining and visualization of the intraepidermal terminals of Adelta and C nerve fibres (Intraepidermal Nerve Fibre Density - IENFD)



• Should be performed in painful/burning feet of unknown origin and clinical impression of small fibre dysfunction

• IENFD shows only a weak negative correlation with the severity of pain

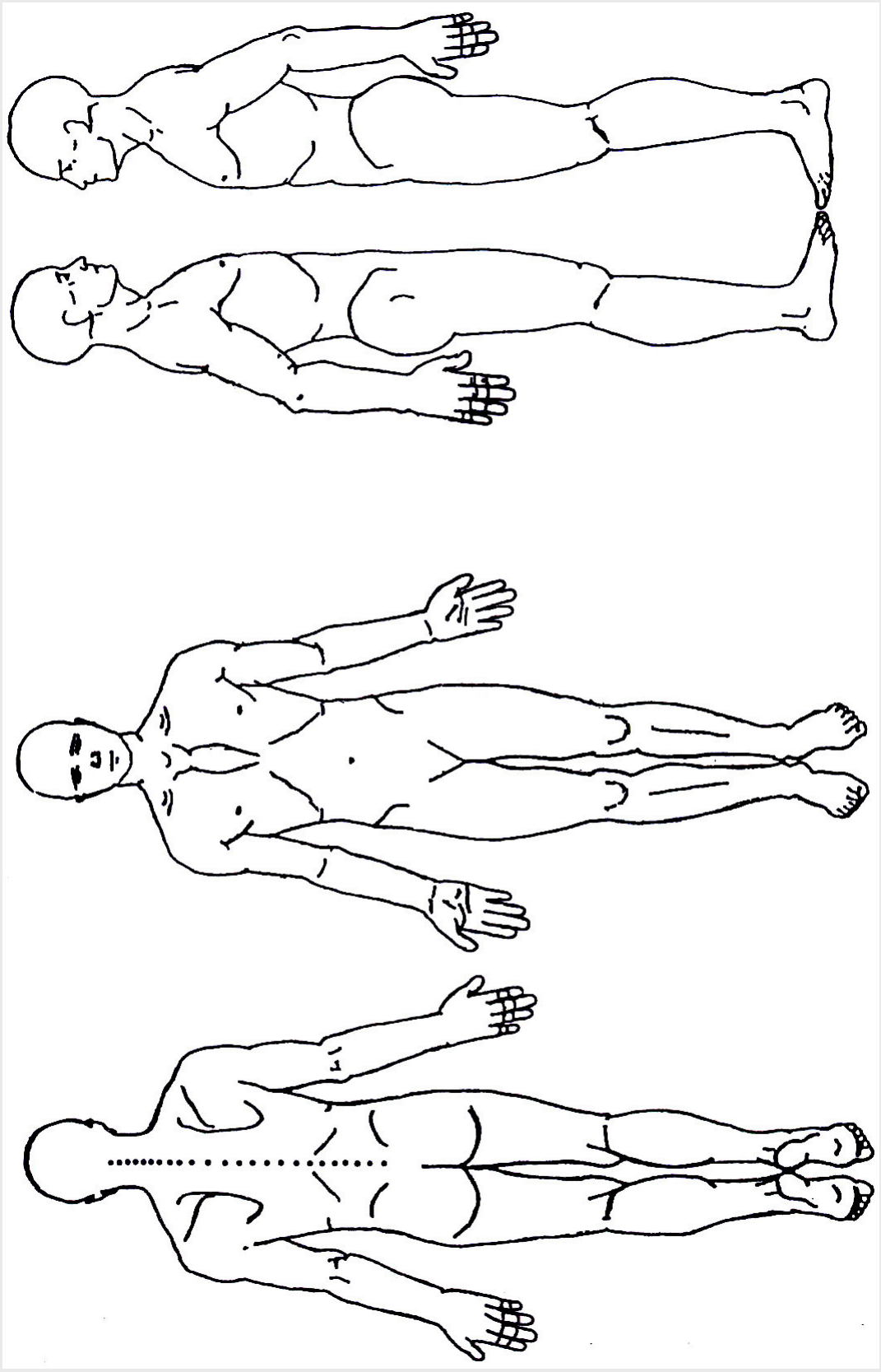
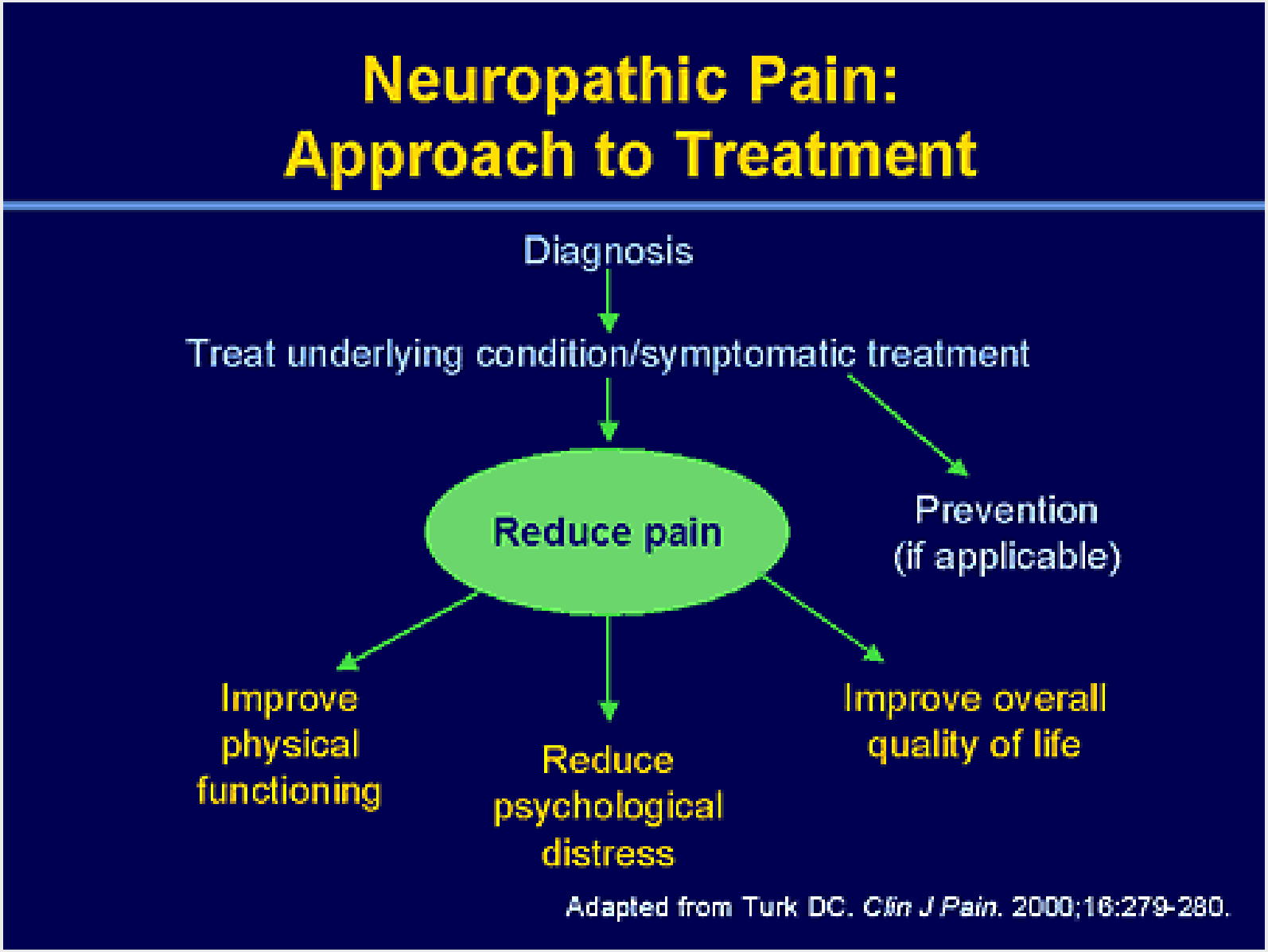


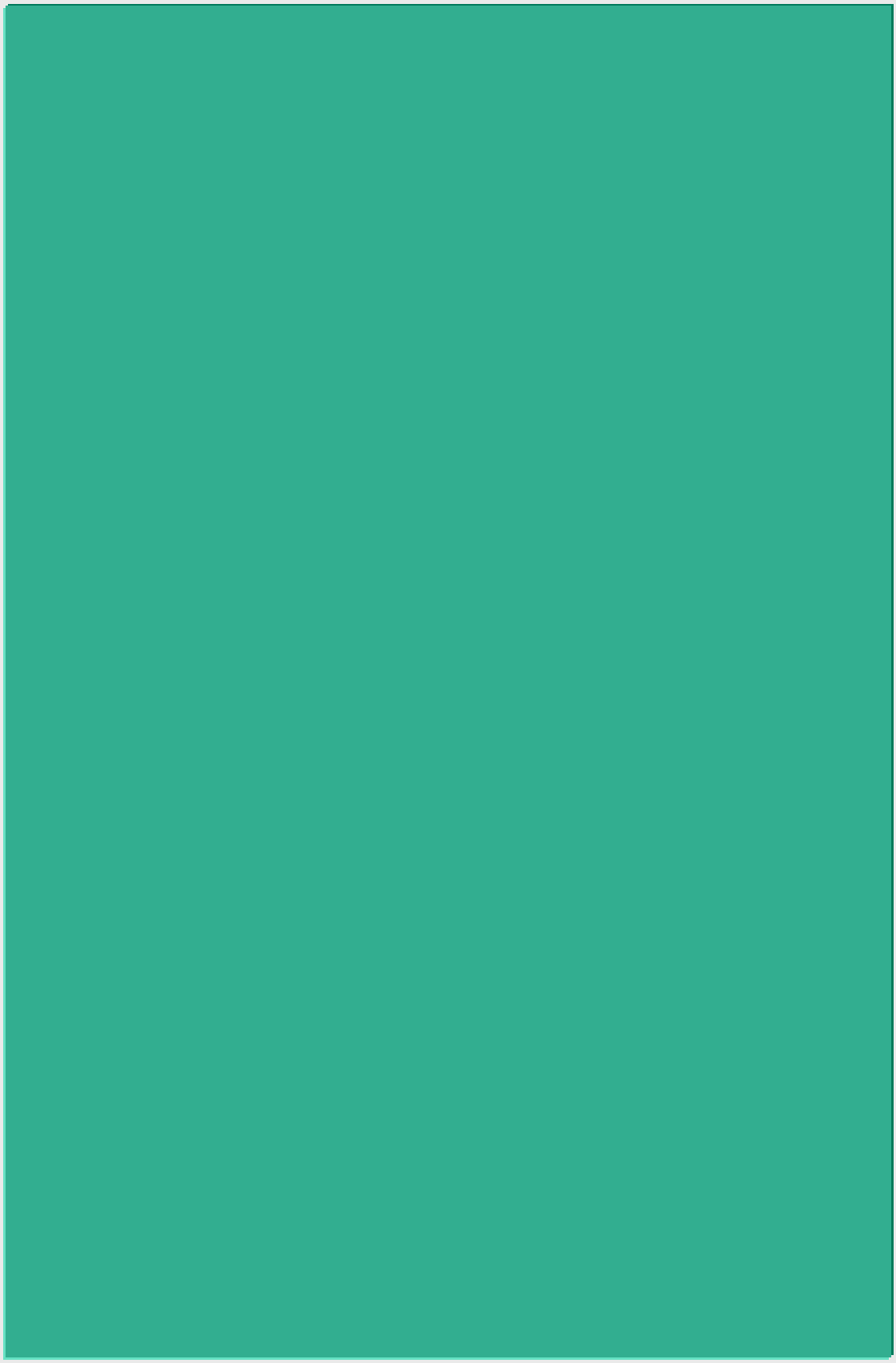
Table II Assessment of positive symptoms and signs during bedside testing and using quantitative sensory testing [36].

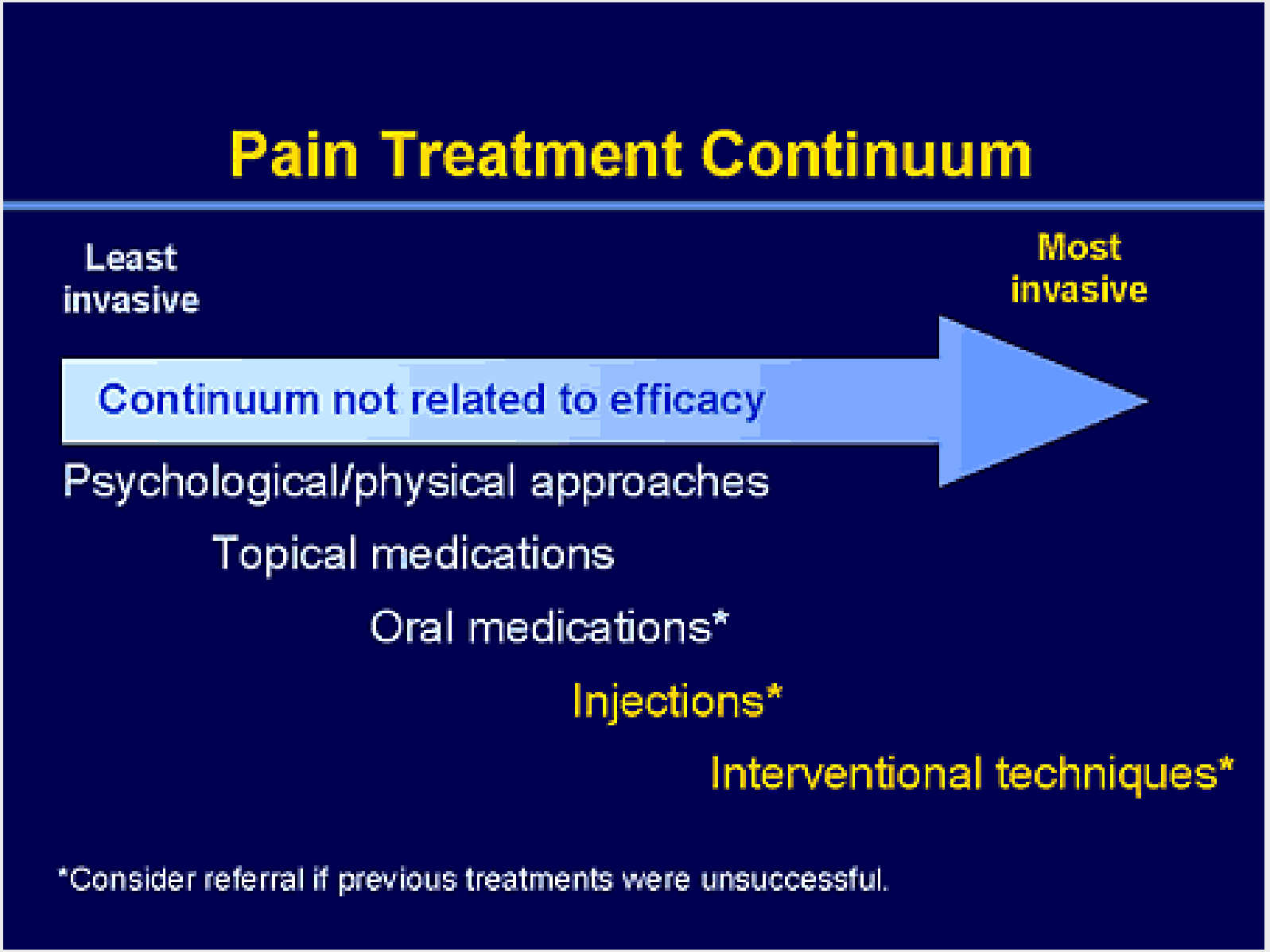
Symptom	Bedside examination	Quantitative sensory test
Dynamic mechanical allodynia	Stroking skin with light tactile stimulus (e.g. brush or cotton wool)	Stroking skin with standardized brush
Punctate hyperalgesia	Pricking skin with pin	Punctate stimulus with von Frey filaments
Static hyperalgesia	Gentle mechanical pressure	Mechanical pressure with, e.g. a pressure algometer
Temporal summation to punctuate stimuli (wind up)	Repetitive pinprick stimuli (e.g. 2/s for 30 s)	Repetitive punctate stimuli with von Frey filaments
Cold hyperalgesia or allodynia	Stimulate skin with cold metal roller or acetone	Threshold determination or pain to graded thermal stimuli using a thermotest
Heat hyperalgesia or allodynia	Stimulate skin with warm metal roller	Threshold determination or pain to graded thermal stimuli using a thermotest

Neuropathic Pain: Approach to Treatment



Adapted from Turk DC. *Clin J Pain*. 2000;16:279-280.




Pain Treatment Continuum
Least invasive
Most invasive
Continuum not related to efficacy
Psychological/physical approaches
Topical medications
Oral medications*
Injections*
Interventional techniques*
*Consider referral if previous treatments were unsuccessful.

Nonpharmacologic Options

- Biofeedback
- Relaxation therapy
- Physical and occupational therapy
- Cognitive/behavioral strategies
  - meditation; guided imagery
- Acupuncture
- Transcutaneous electrical nerve stimulation (TENS)

Interventional Treatments for Neuropathic Pain

- Neural blockade
  - sympathetic blocks for CRPS-I and II (reflex sympathetic dystrophy and causalgia)
- Neurolytic techniques
  - Alcohol or phenol neurolysis
  - pulse radio frequency
- Stimulatory techniques
  - spinal cord stimulation
  - peripheral nerve stimulation
- Medication pumps

Drug	Predominant mechanism
Amitriptyline	TCA, balanced monoamine reuptake inhibition
Capsaicin (topical)	Depolarizes the nervous membrane via vanilloid receptor type 1, initially stimulates then blocks skin nerve fibres
Carbamazepine	Voltage-gated sodium-channel block
Clomipramine	TCA, balanced monoamine reuptake inhibition
Desipramine	TCA, predominantly noradrenaline reuptake inhibition
Dextromethorphan	NMDA-receptor antagonist
Duloxetine	SNRI, serotonin-noradrenaline reuptake inhibition
Gabapentin	Binding to the $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Imipramine	TCA, balanced monoamine reuptake inhibition
Lidocaine (topical)	Block of peripheral sodium channels and thus of ectopic discharges
Lamotrigine	Presynaptic voltage-gated sodium-channel inhibition and thus reduced release of presynaptic transmitters
Memantine	NMDA-receptor antagonist
Nortriptyline	Predominantly noradrenalin reuptake inhibition
Oxcarbazepine	Voltage-gated sodium- and calcium-channel block
Oxycodone	μ-opioid-receptor agonist
Pregabalin	Binding to the $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Tetrahydrocannabinol	Agonist to the CB1 and the CB2 subtype of cannabinoid receptors
Topiramate	Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainate receptors
Tramadol	μ-opioid-receptor agonist and monoamine reuptake inhibitor
Valproate	Increase of GABA levels in brain and potentiation of GABA-mediated responses
Venlafaxine	SNRI, serotonin-noradrenaline reuptake inhibition

Central neuropathic pain

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system

Central post-stroke pain: clinical characteristics, pathophysiology, and management

Lancet Neurol 2009; 8: 857–68

Henriette Klit, Nanna B Finnerup, Troels S Jensen

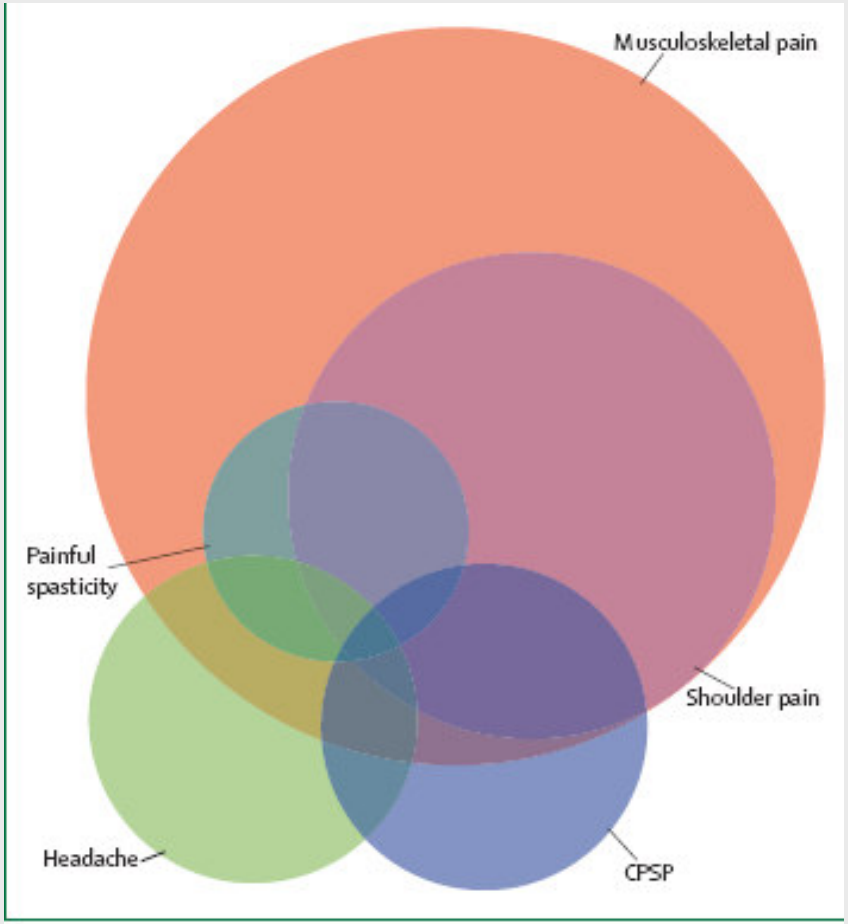


Figure 1: Common types of chronic pain that can occur after stroke

Panel 3: Diagnostic criteria for CPSP

Mandatory criteria for the diagnosis of CPSP

- Pain within an area of the body corresponding to the lesion of the CNS
- History suggestive of a stroke and onset of pain at or after stroke onset
- Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion
- Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely

Supportive criteria

- No primary relation to movement, inflammation, or other local tissue damage
- Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply
- Allodynia or dysaesthesia to touch or cold

CPSP=central post-stroke pain.

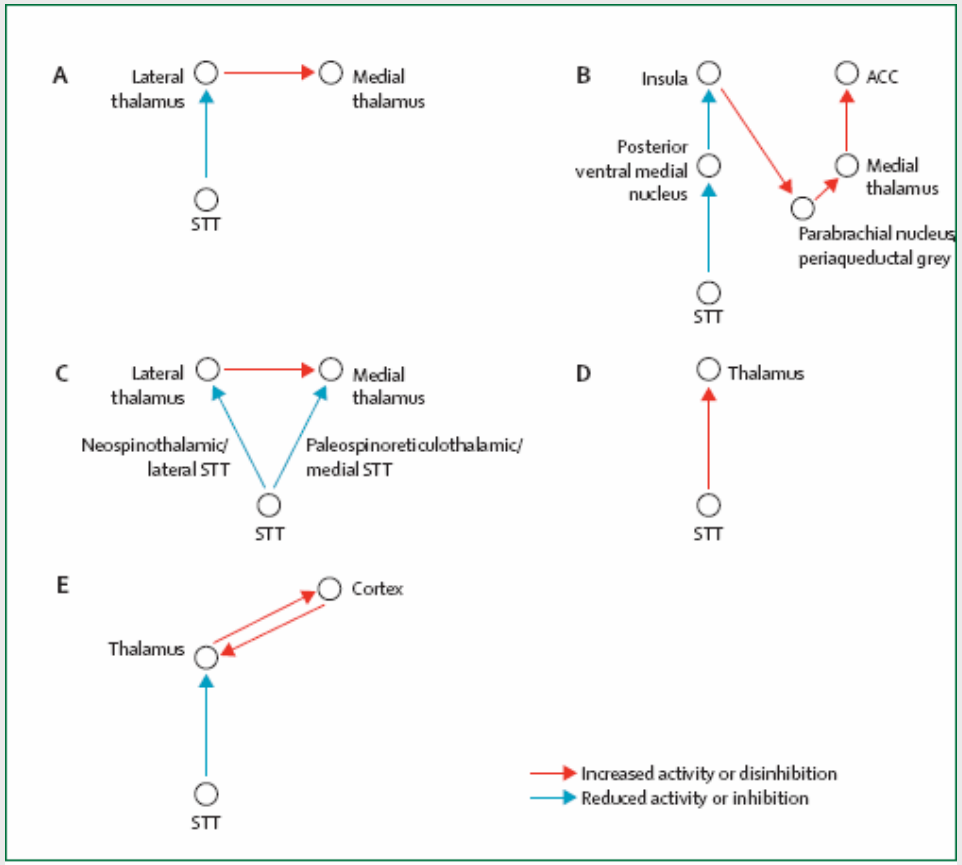


Figure 2: Some proposed mechanisms for central pain

Panel 4: Grading system for CPSP

Criteria to be evaluated for each patient (based on a grading system for neuropathic pain by Treede and co-workers).[11] CPSP is defined as "possible" if criteria 1, 2, and 3 are fulfilled, "probable" if criteria 1, 2, and 3 plus either criteria 4 or 5 are fulfilled, and "definite" if criteria 1–5 are fulfilled.

1 **Exclusion of other likely causes of pain**
No other obvious cause of pain

2 **Pain with a distinct neuroanatomically plausible distribution**
Either pain localised unilaterally in the body and/or face or unilaterally on one side of the body with contralateral involvement of the face

3 **A history suggestive of stroke**
Sudden onset of neurological symptoms with onset of pain at or after stroke onset

4 **Indication of the distinct neuroanatomically plausible distribution by clinical neurological examination**
Findings of positive or negative sensory signs in the painful area on clinical examination, pain localised within a territory of sensory abnormality, and anatomically plausible distribution of sensory abnormalities

5 **Indication of the relevant vascular lesion by imaging**
Visualisation of a lesion that can explain the distribution of sensory findings (either CT or MRI)

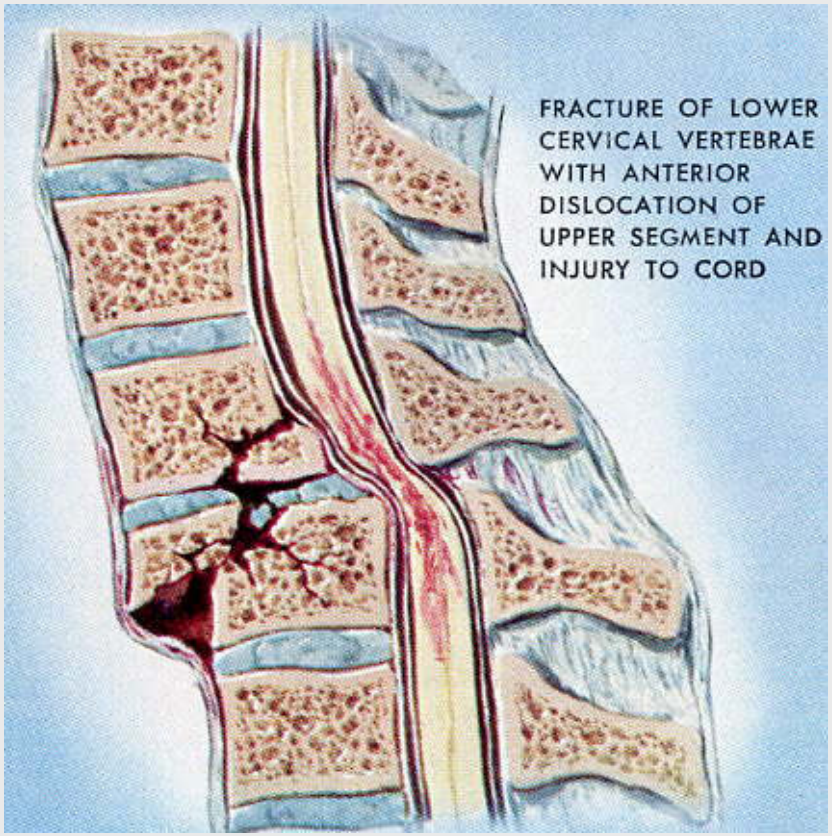
CPSP=central post-stroke pain.

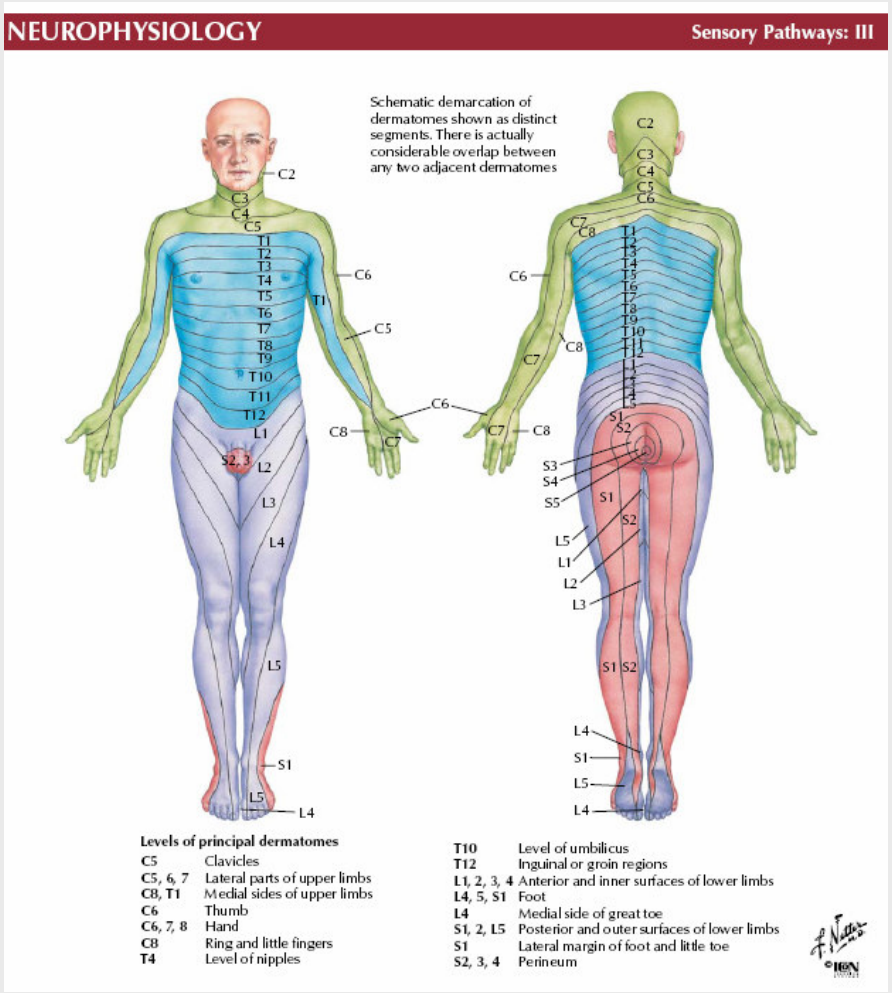
	Dosage (per day)	Outcome	Number of patients	Number of withdrawals	Number needed to treat	Design
Oral and transdermal						
Oral amitriptyline[104]	75 mg	Positive	15 (CPSP)	0	1·7	Three-phase, cross-over
Oral carbamazepine[104]	800 mg	Negative	14 (CPSP)	0	..	Three-phase, cross-over
Oral lamotrigine[105]	200 mg	Positive	30 (CPSP)	10	NA	Cross-over
Oral pregabalin[106]	300–600 mg	Positive	40 (mixed CP: 19 CPSP, 21 SCI)	7	4·0	Parallel, flexible-dose
Transdermal ketamine[107]	50–75 mg	Negative	33 (mixed CP: 15? CPSP)	0	NA	Parallel, three-arm
Intravenous trials						
Morphine[108]	9–30 mg	Negative	15 (mixed CP: 6 CPSP, 9 SCI)	1	NA	Cross-over
Lidocaine[109]	5 mg/kg	Positive	16 (mixed CP: 6 CPSP, 10 SCI)	0	NA	Cross-over
Propofol[110]	0·2 mg/kg	Positive	44 (mixed CP: 22 CPSP)	0	NA	Cross-over
Naloxone[111]	8 mg	Negative	20 (CPSP)	2	NA	Cross-over

..=not applicable. CP=central neuropathic pain. CPSP=central post-stroke pain. NA=not available. SCI=spinal cord injury.

Table 2: **Class I randomised, double-blind, placebo-controlled trials in CPSP**

Pain after spinal cord injury





REVIEW ARTICLE (META-ANALYSIS)

A Systematic Review of Pharmacologic Treatments of Pain After Spinal Cord Injury

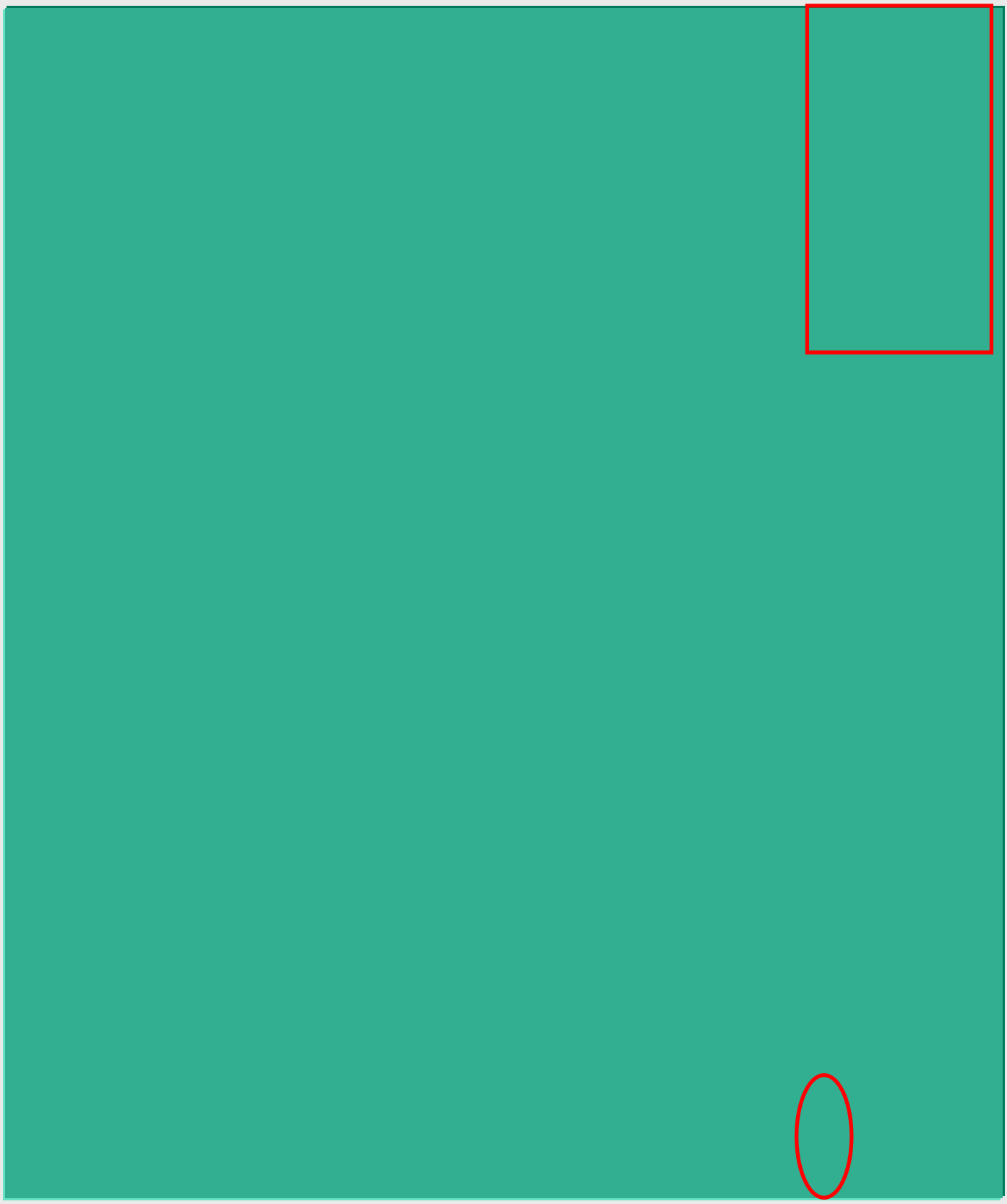
Robert W. Teasell, MD, FRCPC, Swati Mehta, HBSc, Jo-Anne L. Aubut, BA, Brianne Foulon, HBA, Dalton L. Wolfe, PhD, Jane T.C. Hsieh, MSc, Andrea F. Townson, MD, FRCPC, Christine Short, MD, FRCPC, the Spinal Cord Injury Rehabilitation Evidence Research Team

Arch Phys Med Rehabil Vol 91, May 2010

Table 7: Treatment Effectiveness Summary

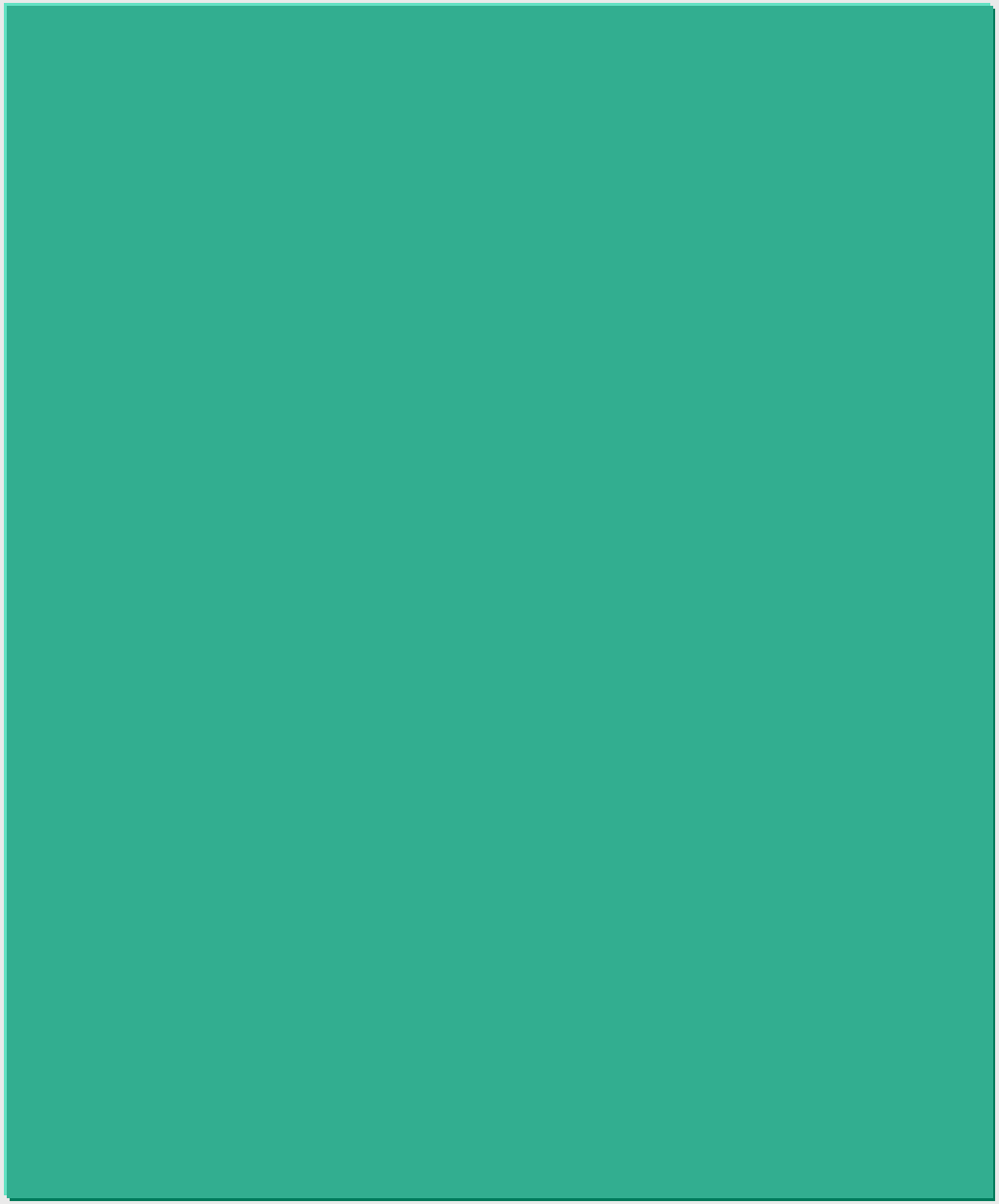
Treatment	Type of Pain	Effectiveness	Level of Evidence
Gabapentin	Neuropathic	+	1
Pregabalin	Neuropathic	+	1
Lamotrigine	Neuropathic	+*	2
Valproic acid	Neuropathic	−	1
Levetiracetam	Neuropathic	−	1
Trazodone	Neuropathic	−	1
Amitriptyline	Neuropathic	+†	1
Lidocaine	Neuropathic	+‡	1
Intravenous ketamine	Neuropathic	+	1
Intravenous alfentanil	Neuropathic	+	1
Intrathecal morphine/ clonidine	Neuropathic/ Mixed	+	1/2
Intravenous morphine	Mixed	+	1
Tramadol	Neuropathic	+	1
Mexilitene	Neuropathic	−	1
Capsaicin	Mixed	+	5
Cannabinoids	Spastic	+/−	2/4
Intrathecal baclofen	Neuropathic	+/−	1/4
Intrathecal baclofen	Musculoskeletal/ Spastic	+	4
Botulinum toxin	Spastic	+	4

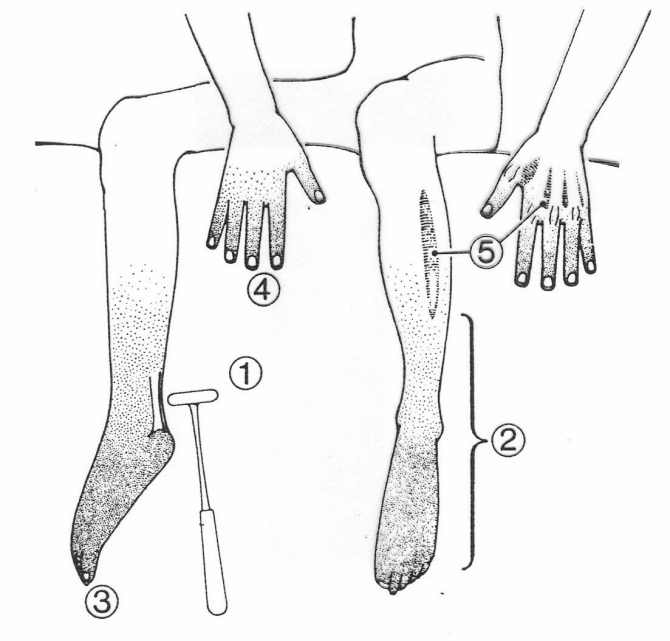
Abbreviation: +, effective; −, not effective; +/−, conflicting.
*Only in persons with incomplete SCI.
†Only in depressed persons.
‡Short-term.

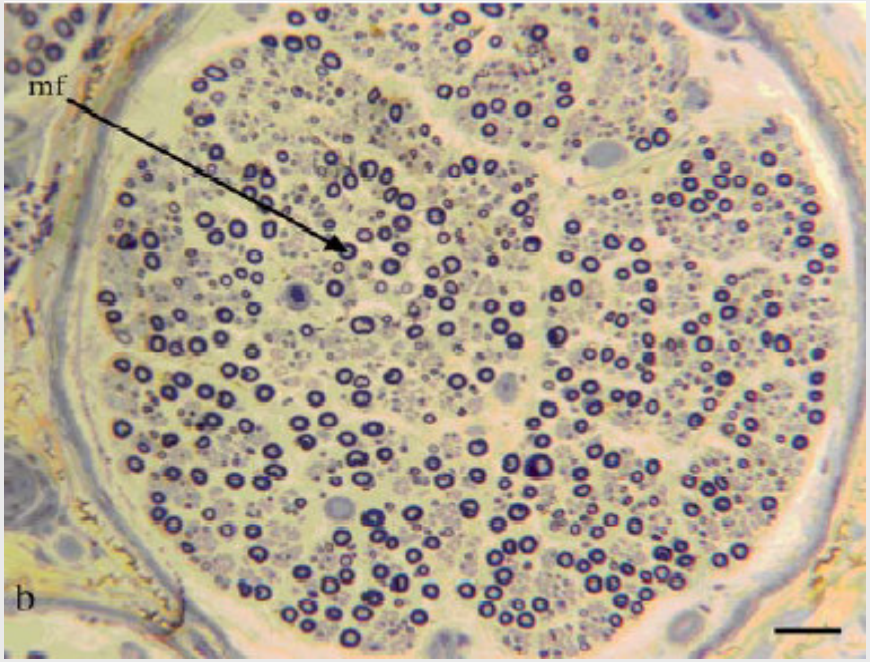


Peripheral neuropathic pain

Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system

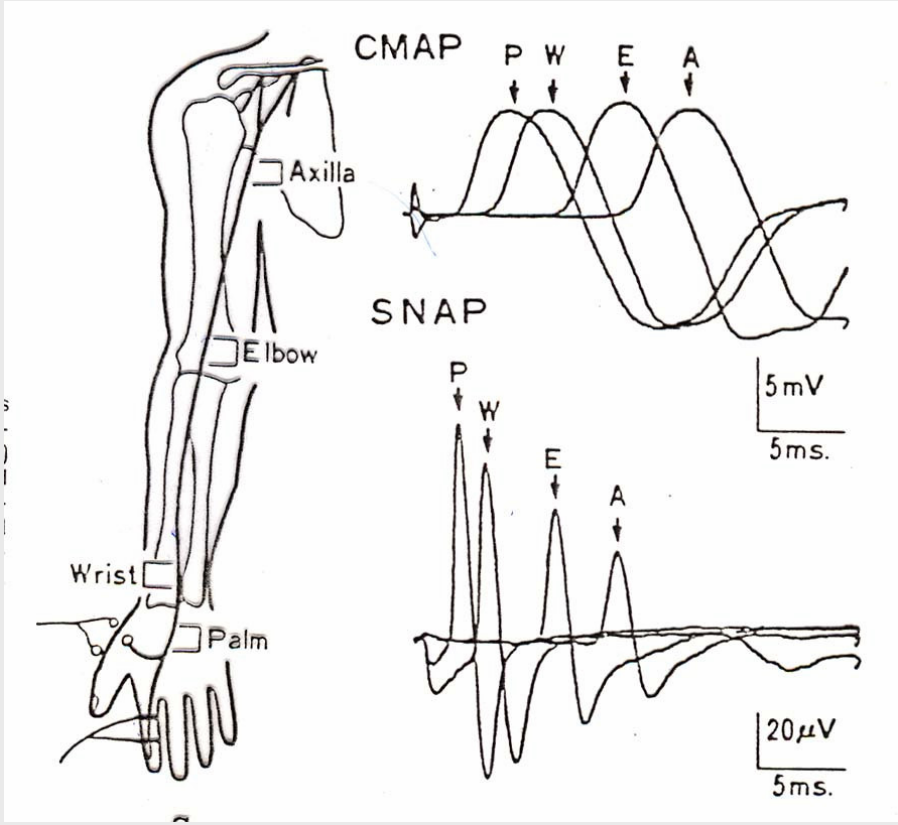


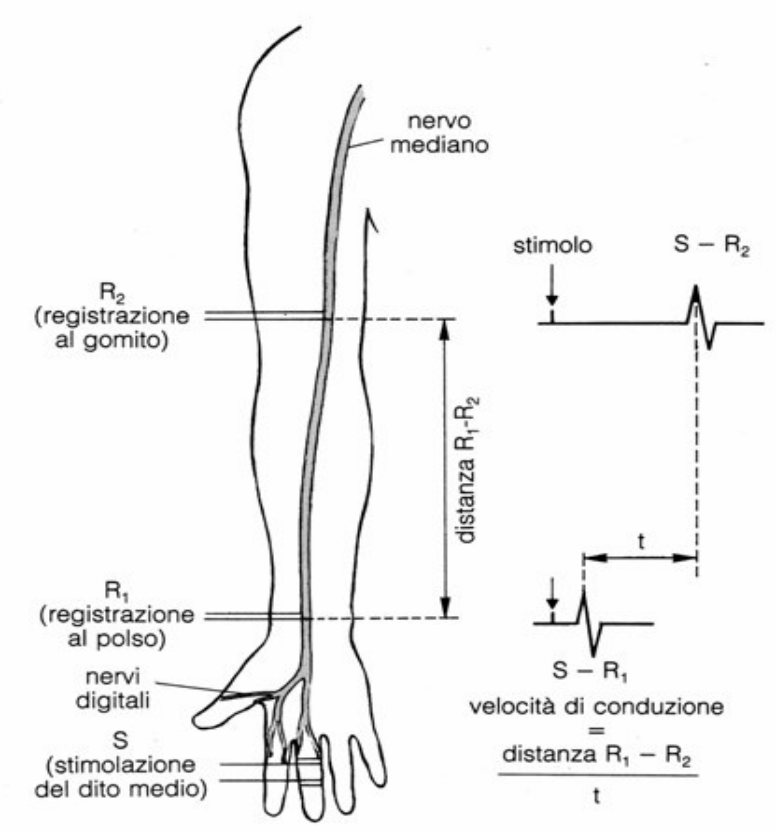




Neuropatia Diabetica

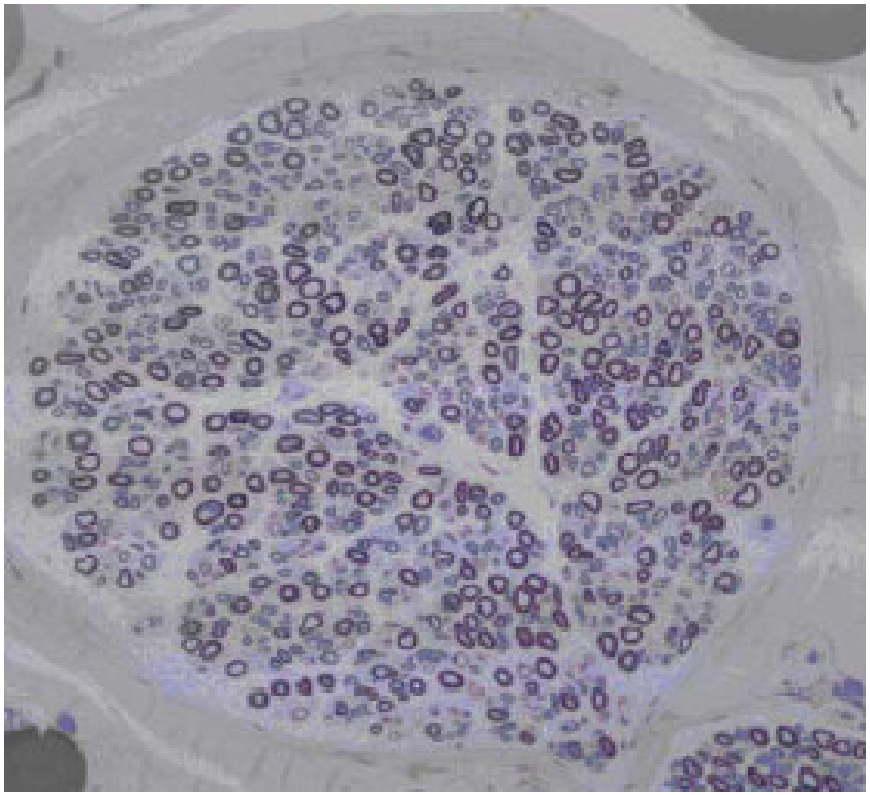
Diagnostica strumentale:
Esame neurografico



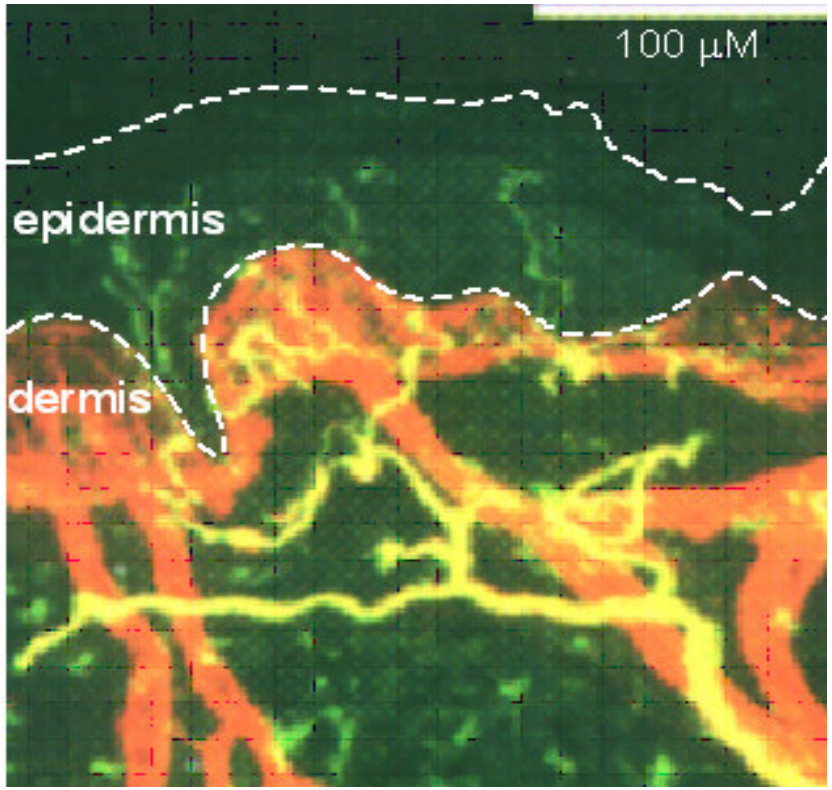


Diagnostica strumentale: Biopsia

Biopsia del nervo surale
ed istogramma delle fibre
nervose di vario calibro



Puntato bioptico della cute
con misurazione della densità di
terminazioni libere



Neuropatia diabetica (I)

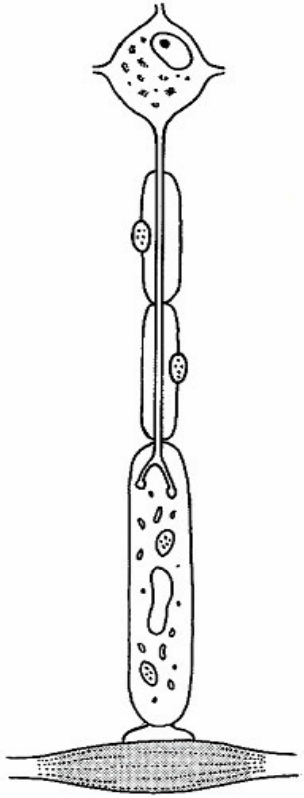
- **Diabete o intolleranza glucidica**
  - 40% dei Nord Americani tra 60 e 74 aa (Harris, Diabetes Care 1998)
  - PNP nel 32% - 50% di diabete vero e 11% di intolleranza

  Diabete non insulino-dipendente
  - Una durata di 10 aa porta la prevalenza di neuropatia dall' 8 al 42% (Partanen, N Engl J Med 1995)
- **Controllo glicemico intensivo**
  - Riduzione del rischio di neuropatia fino al 60 % (DCCT Research Group, Ann Neurol 1995)

Meccanismi fisiopatogenetici

dismetabolico →
(polineuropatie)

ischemico →
(mono- e multi-neuropatie)



assonopatia distale

demielinizzazione
segmentaria

↓

eventuale
degenerazione
Walleriana

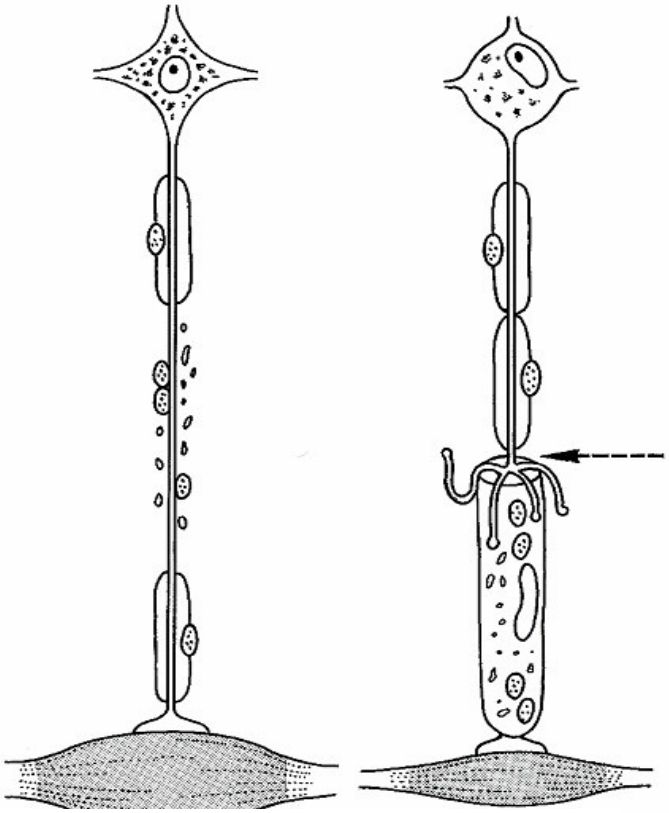


Table 1 Classification of Diabetic Neuropathy

Generalized Neuropathies	Focal or Multifocal Neuropathies
• Distal symmetric polyneuropathy	• Compressive focal neuropathies
○ Large fiber sensory	○ Carpal tunnel syndrome, ulnar neuropathy, peroneal neuropathy
○ Small fiber painful sensory	• Noncompressive focal and multifocal neuropathies
○ Subclinical neuropathy	○ Diabetic amyotrophy
• Acute painful diabetic neuropathy	○ Mononeuritis multiplex
• Autonomic neuropathy	○ Cranial neuropathies
	○ Femoral, sciatic, ulnar, peroneal neuropathy
	○ Truncal neuropathies

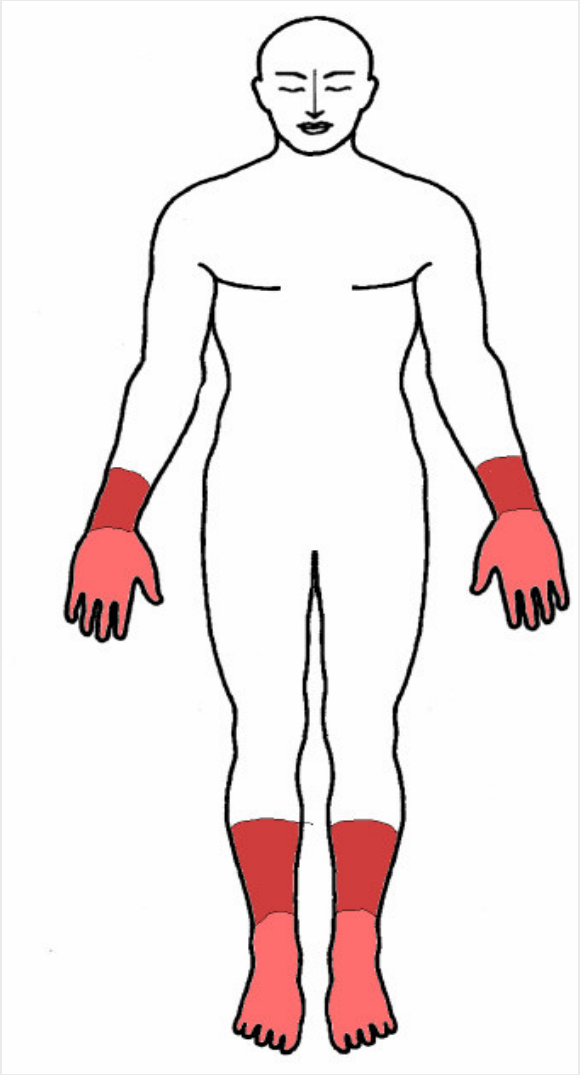
Polineuropatie dismetaboliche

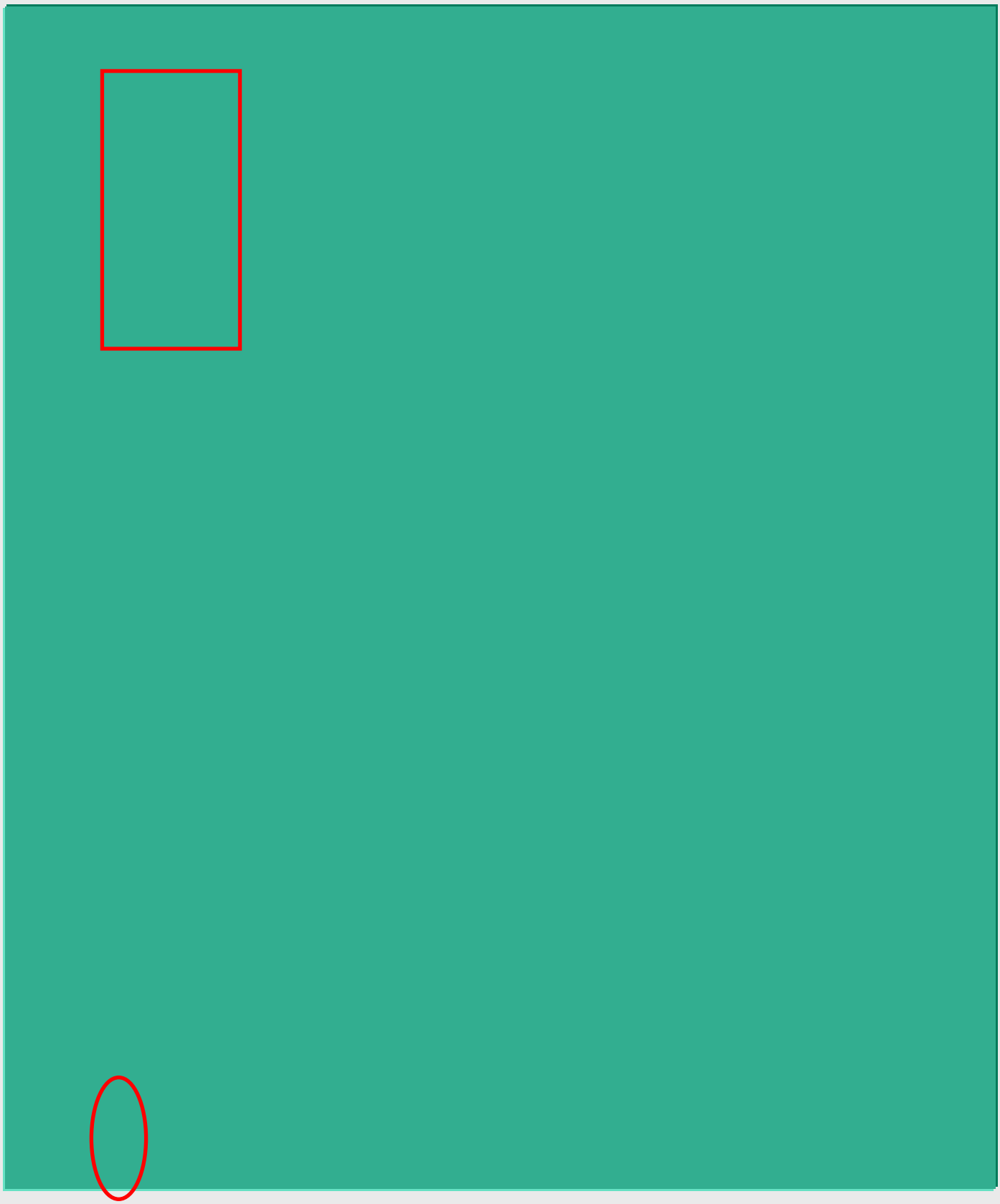
Forme cliniche:

- **Polineuropatia sensori-motoria**
- **Polineuropatia delle piccole fibre**
- **Polineuropatia disautonomica**

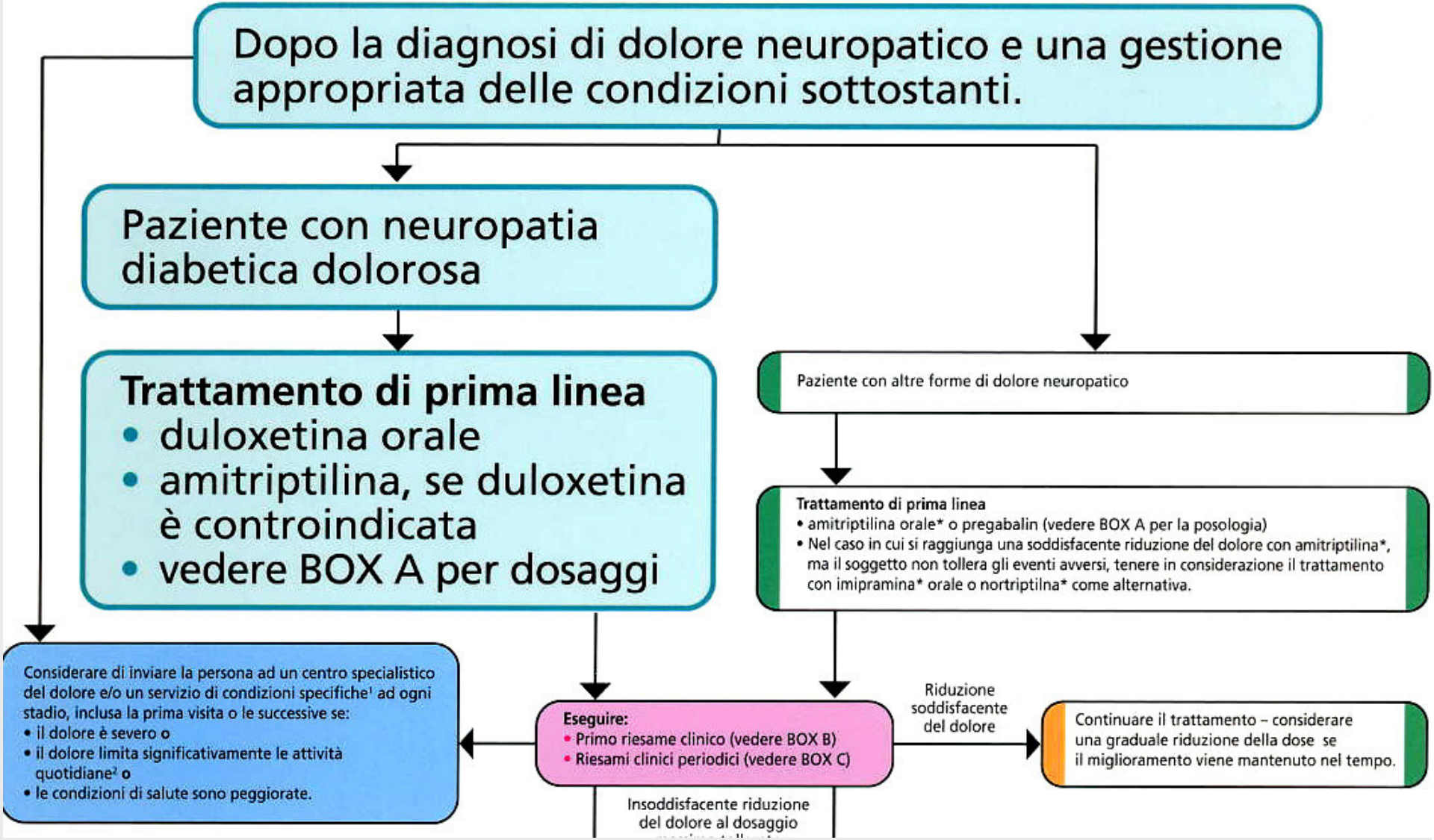
Dovute a difetto dei meccanismi di trasporto assoplasmatico. La porzione distale dell'assone, più lontana dal centro trofico, degenera, e il danno risale progressivamente. Sono colpiti per primi gli assoni più lunghi e quelli di maggior diametro che hanno una richiesta metabolica maggiore.

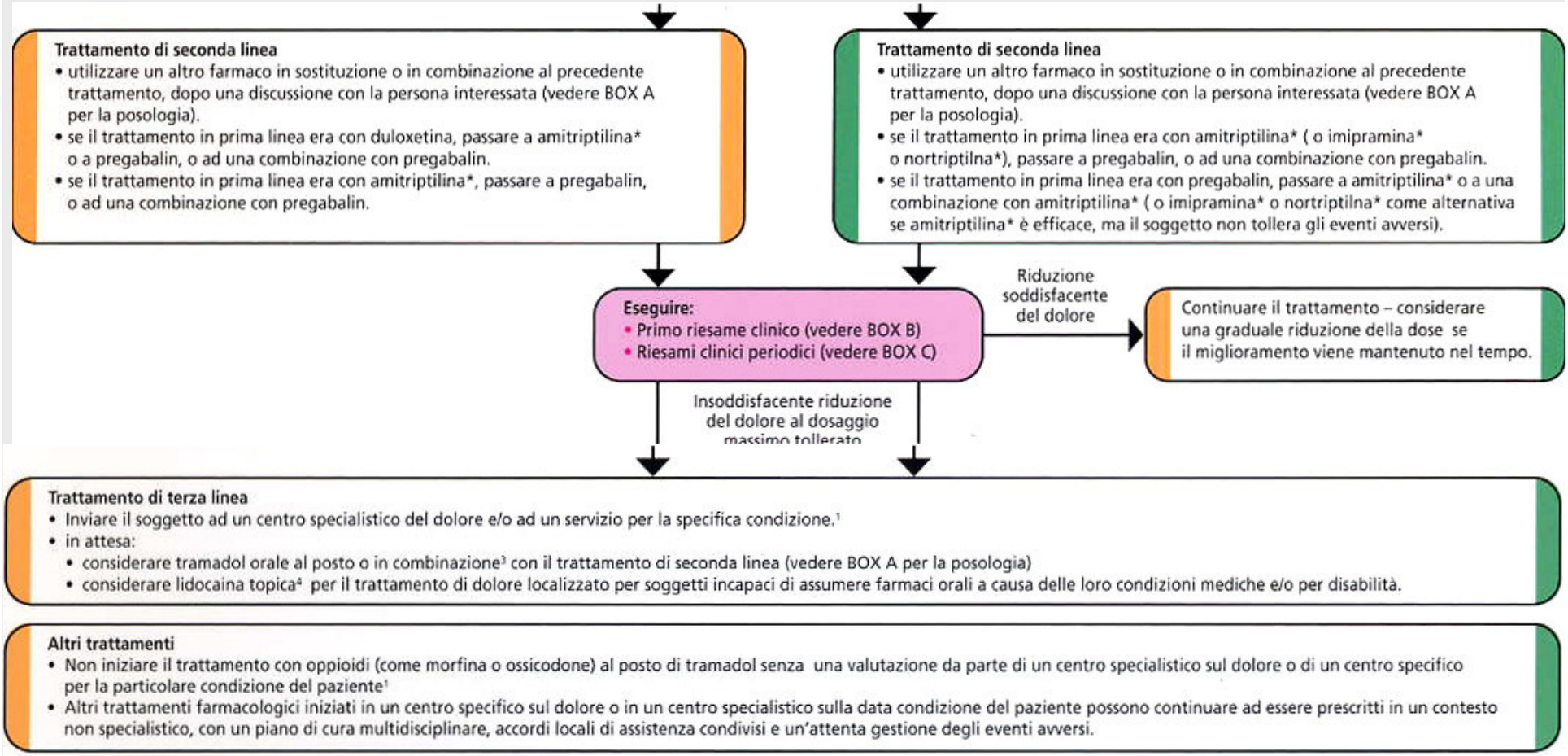
Nelle assonopatie simmetrico-distali il disturbo sensitivo è disposto a "calza" o a "calza e guanto"





Scheda di trattamento[1]




Trattamento di seconda linea
• utilizzare un altro farmaco in sostituzione o in combinazione al precedente trattamento, dopo una discussione con la persona interessata (vedere BOX A per la posologia).
• se il trattamento in prima linea era con duloxetina, passare a amitriptilina* o a pregabalin, o ad una combinazione con pregabalin.
• se il trattamento in prima linea era con amitriptilina*, passare a pregabalin, o ad una combinazione con pregabalin.
Trattamento di seconda linea
• utilizzare un altro farmaco in sostituzione o in combinazione al precedente trattamento, dopo una discussione con la persona interessata (vedere BOX A per la posologia).
• se il trattamento in prima linea era con amitriptilina* (o imipramina* o nortriptilna*), passare a pregabalin, o ad una combinazione con pregabalin.
• se il trattamento in prima linea era con pregabalin, passare a amitriptilina* o a una combinazione con amitriptilina* (o imipramina* o nortriptilna* come alternativa se amitriptilina* è efficace, ma il soggetto non tollera gli eventi avversi).
Eseguire:
• Primo riesame clinico (vedere BOX B)
• Riesami clinici periodici (vedere BOX C)
Riduzione soddisfacente del dolore
Continuare il trattamento – considerare una graduale riduzione della dose se il miglioramento viene mantenuto nel tempo.
Insoddisfacente riduzione del dolore al dosaggio massimo tollerato
Trattamento di terza linea
• Inviare il soggetto ad un centro specialistico del dolore e/o ad un servizio per la specifica condizione.[1]
• in attesa:
• considerare tramadol orale al posto o in combinazione[3] con il trattamento di seconda linea (vedere BOX A per la posologia)
• considerare lidocaina topica[4] per il trattamento di dolore localizzato per soggetti incapaci di assumere farmaci orali a causa delle loro condizioni mediche e/o per disabilità.
Altri trattamenti
• Non iniziare il trattamento con oppioidi (come morfina o ossicodone) al posto di tramadol senza una valutazione da parte di un centro specialistico sul dolore o di un centro specifico per la particolare condizione del paziente[1]
• Altri trattamenti farmacologici iniziati in un centro specifico sul dolore o in un centro specialistico sulla data condizione del paziente possono continuare ad essere prescritti in un contesto non specialistico, con un piano di cura multidisciplinare, accordi locali di assistenza condivisi e un'attenta gestione degli eventi avversi.

BOX A: Posologia

- Iniziare la terapia con una dose inferiore, come indicato in tabella.
- Aumentare gradualmente il dosaggio fino ad una dose efficace o alla dose massima tollerata (non superare la dose massima indicata in tabella).

Farmaco	Dose iniziale	Dose massima
Amitriplina	10 mg/die	75 mg/die[a]
Pregabalin	150 mg/die[b] (suddivisi in due somministrazioni)	600 mg/die (suddivisi in due somministrazioni)
Duloxetina	60 mg/die[b]	120 mg/die
Tramadol[c]	50-100 mg al massimo ogni 4 ore	400 mg/die

[a] Dosi più elevate possono essere prese in considerazione con uno specialista del dolore.
[b] Dosi iniziali inferiori potrebbero essere consigliate in alcuni pazienti.
[c] In monoterapia. Una titolazione più conservativa potrebbe essere richiesta in caso di terapia in associazione.

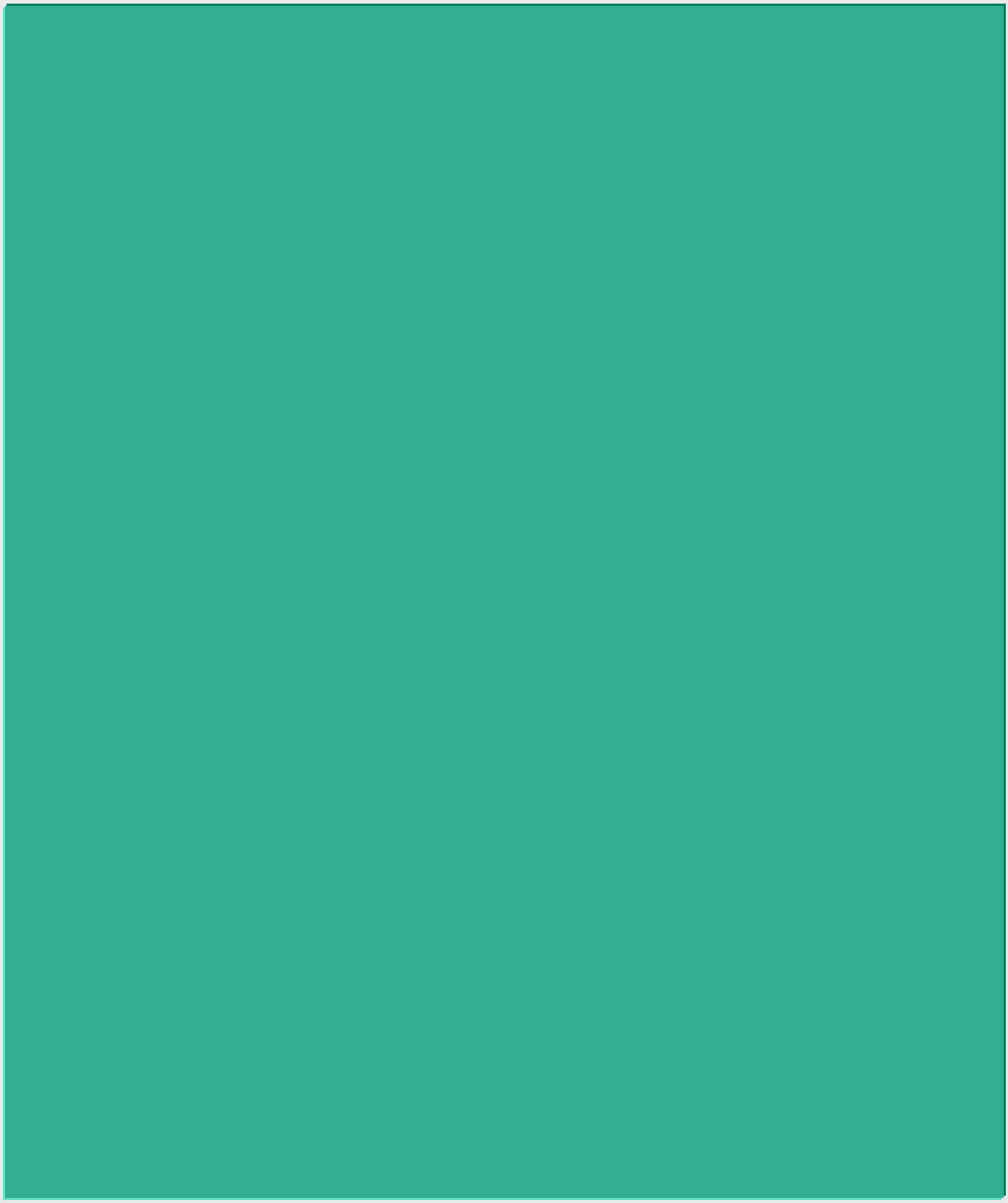
BOX B – Primo riesame clinico.

Dopo l'inizio o la modifica di una terapia, eseguire un primo riesame clinico per titolare il dosaggio, valutare la tollerabilità e gli eventi avversi, così da verificare l'idoneità del trattamento scelto.

BOX C – Riesami clinici periodici

Effettuare riesami clinici periodici per monitorare l'idoneità del trattamento scelto. Valutare:

- riduzione del dolore
- eventi avversi
- partecipazione alle attività quotidiane[2] (es: capacità di lavorare o guidare)
- umore (in particolare possibile depressione e/o stati di ansia[5])
- qualità del sonno
- miglioramento generale come riportato dal soggetto.

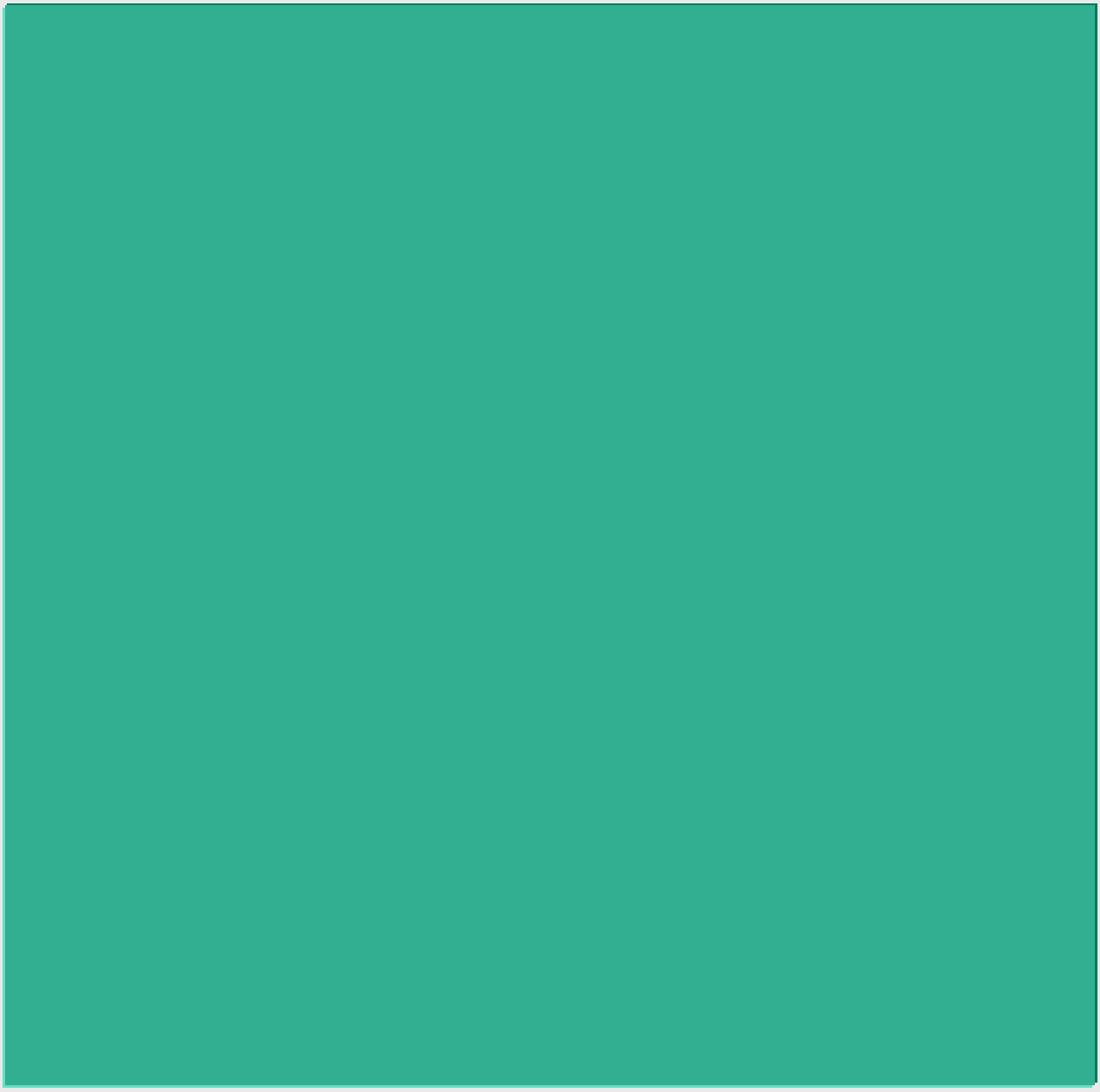


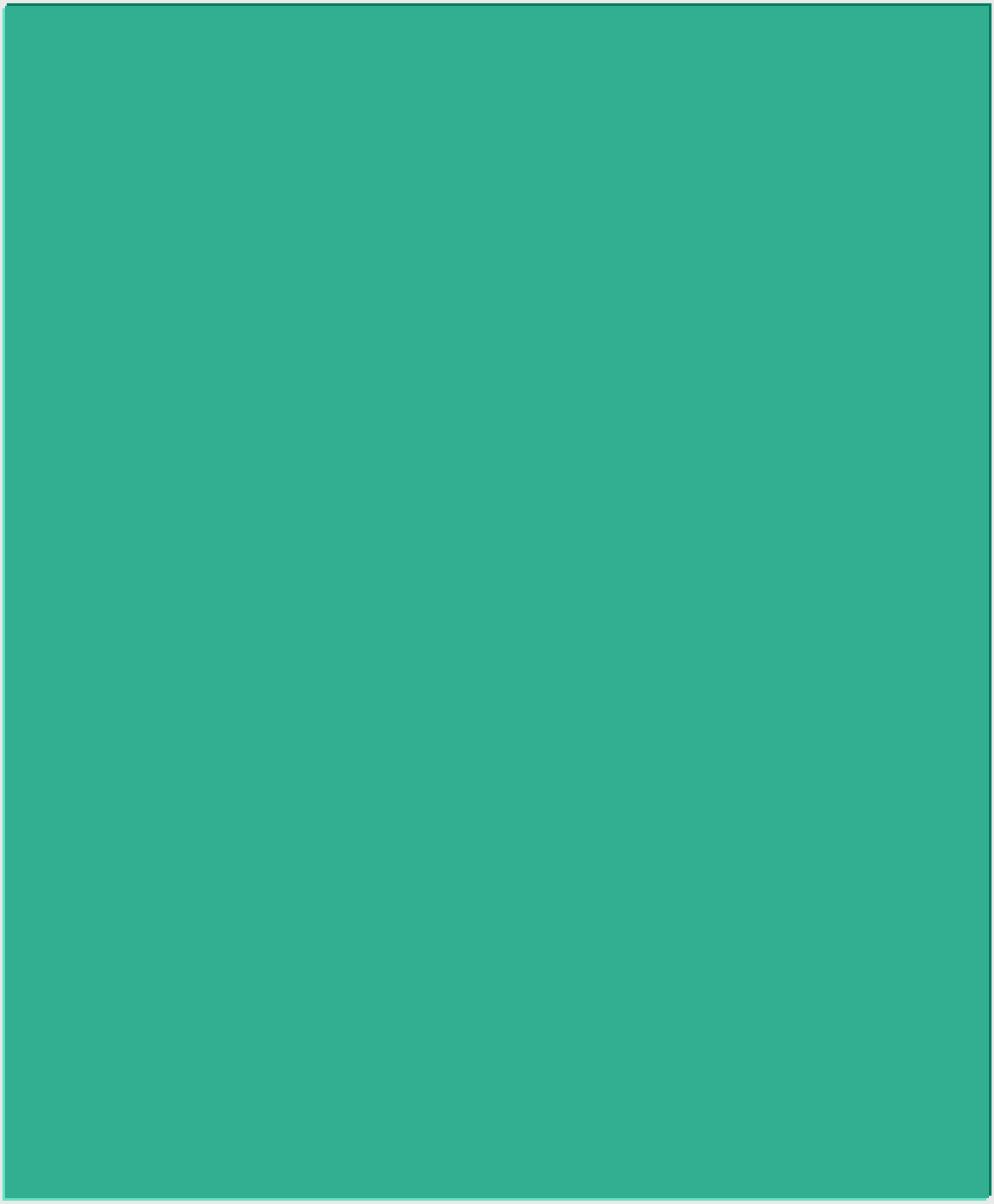
Complex Regional Pain Syndrome II

CRPS 2 formerly known as ***causalgia***,

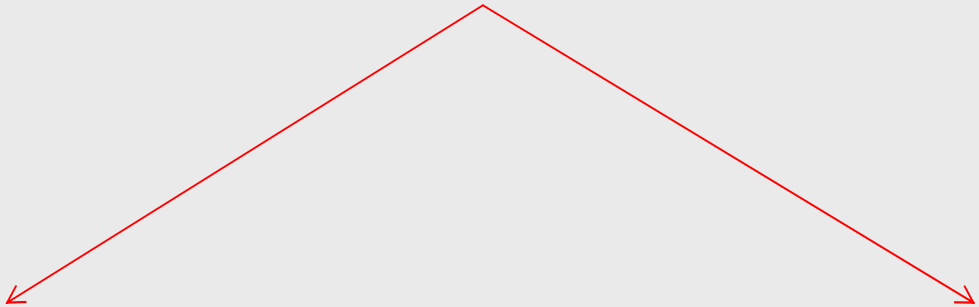
Complex Regional Pain Syndrome I

CRPS I formerly known as ***reflex sympathetic dystrophy***



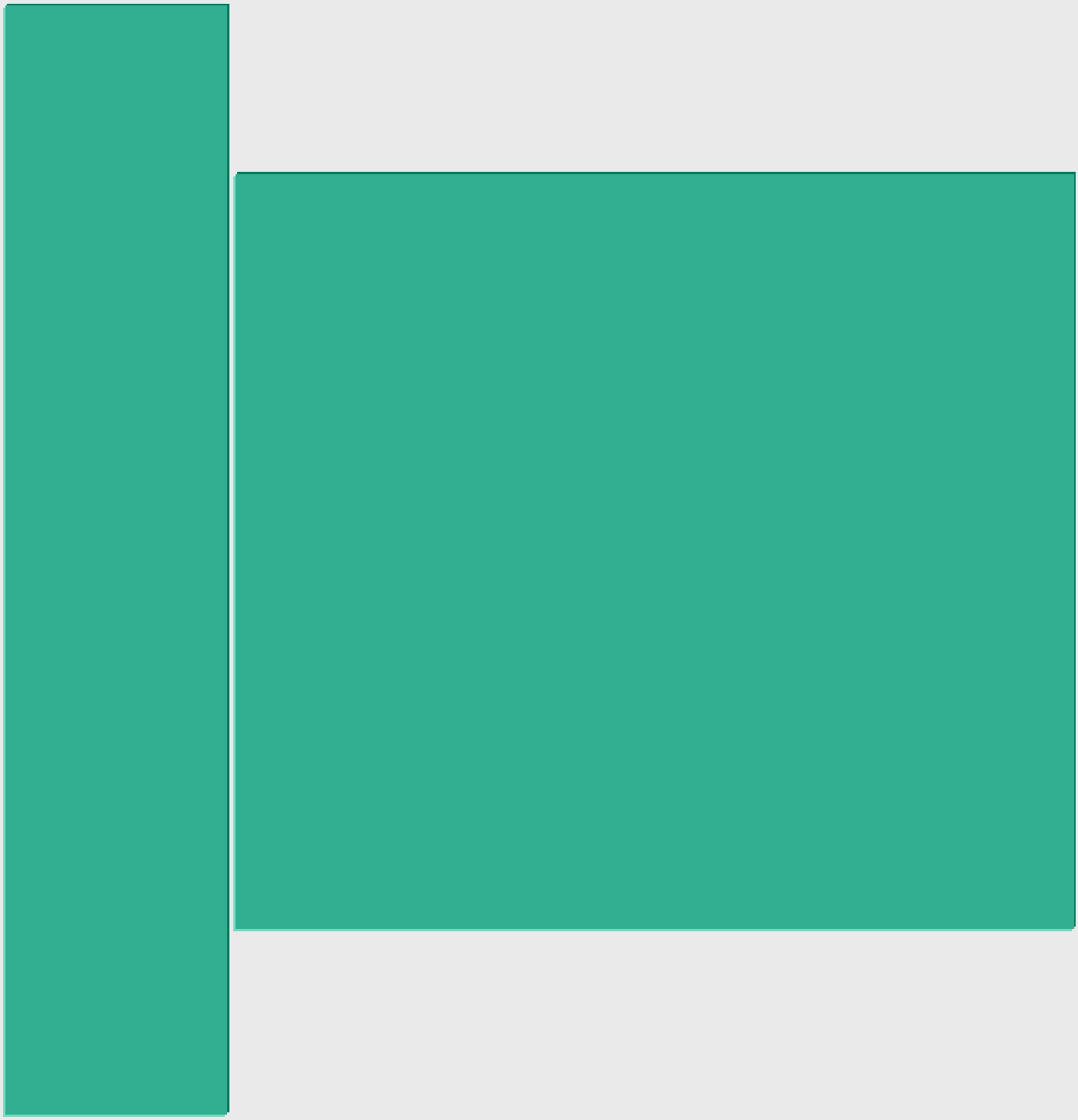


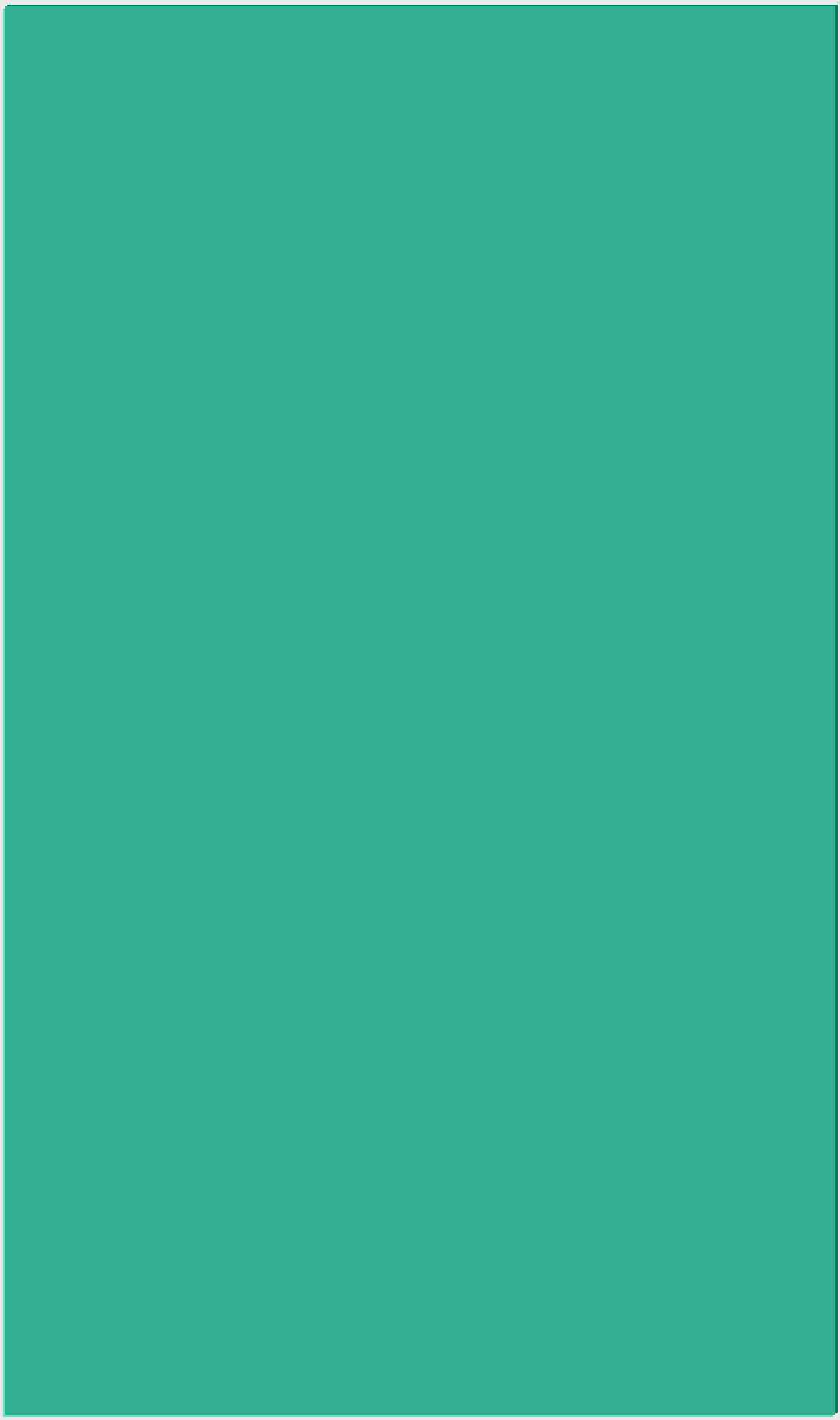
Neurosurgical treatments of intractable pain



Ablative neurosurgery

Nonablative neurosurgical interventions





Recommendations

• Standard high-frequency **TENS** is possibly better than placebo (level C) though probably worse than acupuncture-like (level B)

• We found level B evidence for the effectiveness of **SCS** in **FBSS** and **CRPS I**. The available evidence is also positive for CRPS II, peripheral nerve injury, diabetic neuropathy, PHN, brachial plexus lesion, amputation (stump and phantom pains) and partial spinal cord injury

• For the use of **DBS** there is weak positive evidence in peripheral neuropathic pain including pain after amputation and facial pain. In CPSP results are equivocal

• There is level C evidence that **MCS** is useful in 50–60% of patients with **CPSP** and central or peripheral facial neuropathic pain

• There is moderate evidence that **rTMS** of the motor cortex, using a figure-of-eight coil and high frequency (5–20 Hz) induces significant pain relief in **CPSP** and several other neuropathic pain conditions (level B). It may be proposed for **shortlasting pains** or to **identify suitable candidates** for an epidural implant (MCS). In contrast, low-frequency rTMS is probably ineffective (level B).