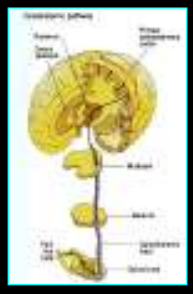
Neuropathic Pain Definition

Pain which originates from disruption (lesion) of the somato-sensory nervous system



Neuropathic Pain Classification

Central:

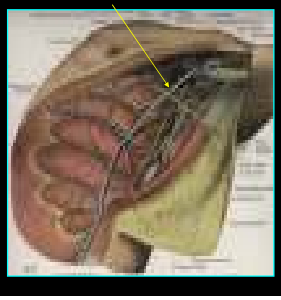
- Post stroke pain
- Post spinal-cord injury
- Pain in MS

Peripheral:

- Diabetic neuropathy
- Post-herpetic neuralgia
- Post nerve injury pain
- Stump pain
- Phantom pain
- Complex regional pain syndrome (type II)
- Other painful peripheral neuropathies

Post-Mastectomy Pain Syndrome

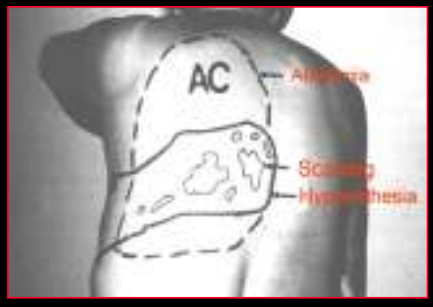
Intercosto-brachial nerve



Stump & Phantom Pain

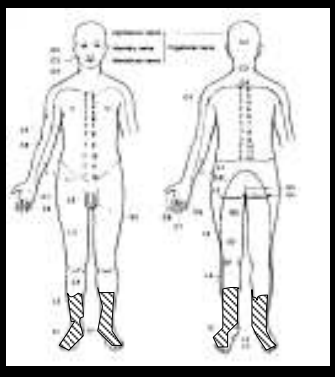
Complex Regional Pain Syndrome
(CRPS known also as RSD)

Post Herpetic Neuralgia



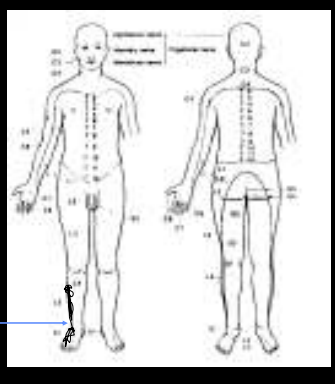
A 2-Year Old CRPS-I

Pain Drawing



Symmetrical
Polyneuropathy

Pain Drawing



Rt. Peroneal Neuropathy

Neuropathic Pain

History:

- May have delayed onset
- Often no visible injury
- Severe intensity, Variable qualities
- Additional neurological complaints
- Resistant to treatment
- Significant effect on QOL

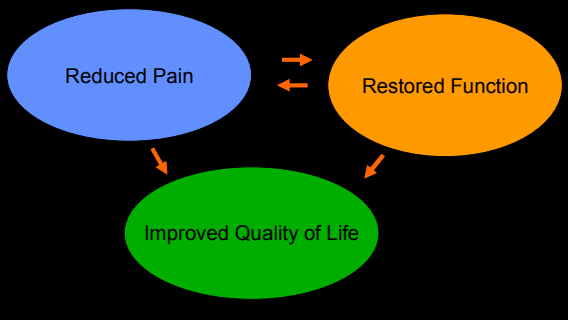
Neuropathic Pain

Bedside Clinical Examination:

+ Hyperalgesia / allodynia
+ Tinel sign
+ 'Wind-up' like pain
- Sensory loss
+/- Autonomic dysfunction
- Motor weakness
- Atrophy / dystrophy
+ Tremor, dystonia
+/- Changes in tendon reflexes

Treatment

Chronic Pain – Goals of Treatment



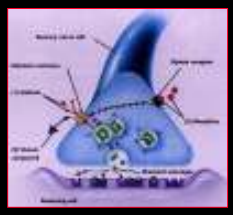
Neuropathic Pain Treatment

- Pharmacology
- Physical treatments
- Psychological support
- Procedures

Neuropathic Pain Treatment

Pharmacological treatments:

- Antidepressants
- Anticonvulsants
- Opioids
- Ion channel blockers
- NMDA receptor antagonists
- Capsaicin, other topical agents
- Other (GABA-B agonists, calcitonin, levodopa, steroids)



Neuropathic Pain Treatment

Antidepressants:

- TCAs
- SSRI
- SNRI

Numbers Needed to Treat – NNT

The number of patients needed to be treated with a certain drug, in order to obtain one patient with a defined degree of pain relief

$$\frac{1}{\frac{\text{goal achieved}_{\text{active}}}{\text{total}_{\text{active}}} - \frac{\text{goal achieved}_{\text{placebo}}}{\text{total}_{\text{placebo}}}}$$

Cook & Sackett BMJ '95

Antidepressants:

TCAs: (amitriptyline; cloripramine)

- Dose: 10-150 mg; x1; bedtime
- Slow titration
- NNT 3.1
- Multiple adverse effects (anticholinergic; ECG)
- C.I.: sensitivity, glaucoma, prostate, prolonged Q-T

Antidepressants:

SSRI: (paroxetine)

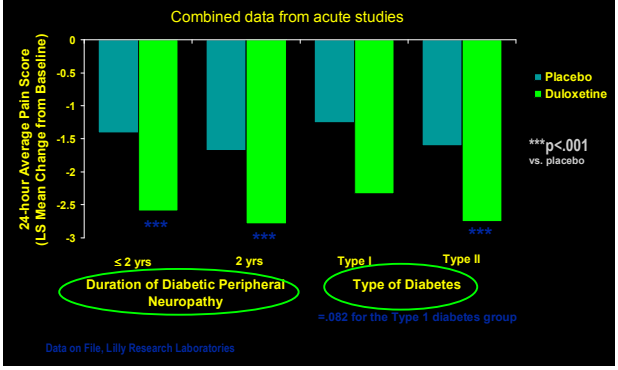
- Dose: 10-20 mg (rarely 40-60); x1; morninng
- Faster titration
- NNT 6.7
- Fewer adverse effects (sexual dysfunction; weigh gain; habituating)

Antidepressants:

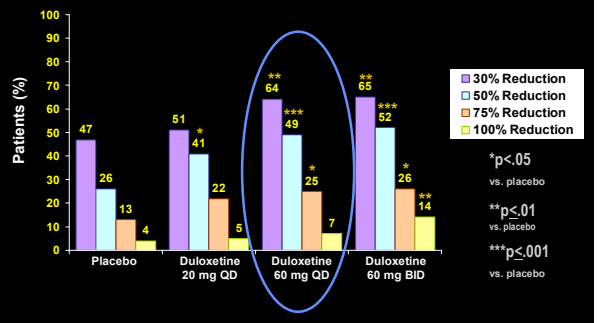
SNRI: (duloxetine, venlafaxine)

- Indication: PDN
- Dose: duloxetine 60 mg (30); x1; pm/am
  venlafaxine 75-225 mg
- Second line
- No titration
- NNT ~ 4.0
- Adverse effects: (sedation, nuasea)
- C.I.: sensitivity, elevated LFTs

Duloxetine: 24-hour Average Pain Score

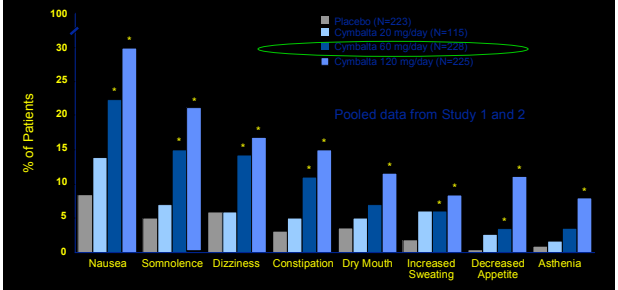


Duloxetine: 24-hour Average Pain Response Rates at Endpoint



Goldstein DJ, et al. Pain 116 (2005) 109-118

Duloxetine – safety profile short term studies (12 w)



Adverse events that occurred ≥5% with Cymbalta (20-120 mg/day) and at least twice the rate of placebo

Neuropathic Pain Treatment

Anticonvulsants:

- carbamazepine
- clonazepam
- phenytoin
- sodium valproate
- gabapentin
- lamotrigine
- topiramate
- pregabalin

Anticonvulsants :

Carbamazepine: (tegretol; teril)

- Dose: 200-600 mg; x 2-3 /day
- Slow titration
- NNT 2.0
- Adverse effects (CNS; liver, WBC, low Na^+)

Anticonvulsants :

Gabapentin: (Neurontin; Gabapentine)

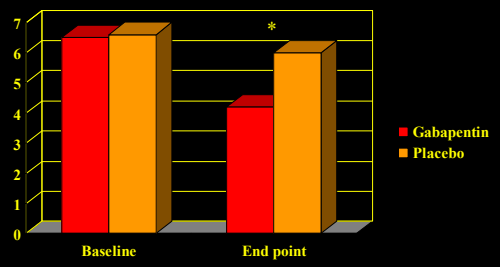
- First line
- Dose: 300-1200 mg; x 3 /day
- Fast titration
- NNT 4.0
- Adverse effects (CNS; edema)

Gabapentin for PHN

- Multicenter, randomized, double-blind, placebo-controlled trial
- 229 PHN patients were randomized to receive gabapentin (n = 113) or placebo (n = 116)
- 4 weeks titration period + 4 weeks fixed-dose period

Backonja et al. JAMA '98

Gabapentin for PHN:
Change in Average Daily Pain Score



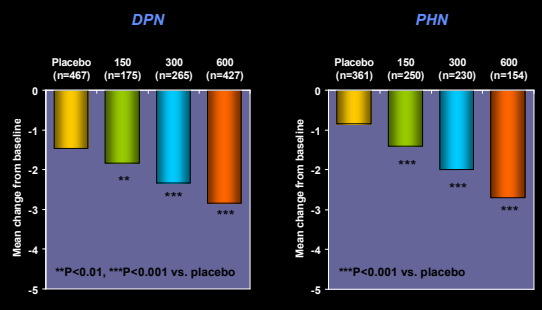
* P< 0.001; final dose ≥ 2400mg in >90% of patients

Anticonvulsants :

Pregabalin: (Lyrica)

- First line
- Dose: 75-300 mg; x 2 /day
- Fast titration
- NNT: ?
- Adverse effects (CNS, edema, weigh gain)

Pain Relief in DPN and PHN



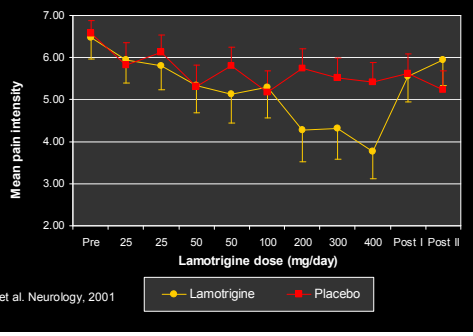
DPN patients from 6 studies, PHN patients from 5 studies pooled
Data on file, Pfizer Inc

Anticonvulsants :

Lamotrigine: (Lamictal)

- Dose: 400 mg; x 2 /day
- Slow titration
- NNT 4.9
- Adverse effects (CNS; rash)
- Not reimbursable

Lamotrigine in Diabetic Neuropathy



Eisenberg et al. Neurology, 2001

Neuropathic Pain Treatment

Opioids:

- Codeine
- Propoxyphene
- Tramadol
- Morphine
- Oxycodone
- Fentanyl
- Methadone

Opioids for PHN

Study: Watson et al. Neurology 1998

Patients: 50 elderly patients, PHN

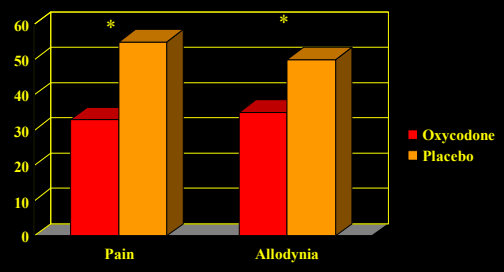
Design: RCT, Oxycodone 60 mg, 4 weeks

Results: significantly ↓ pain & allodynia

AE's: not serious

Opioids for PHN

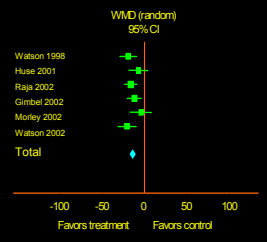
Watson et al. Neurology 1998



* P< 0.001; final week of treatment

Opioids Vs. Placebo for Neuropathic Pain: A Meta-analysis of RCTs

Outcome: Pain intensity (VAS) after treatment



Endpoint opioid VAS: -13.8 points (95% C.I. -18.4 -9.2) compared to placebo; p<0.00001

Eisenberg et al., JAMA 2005

NNT- Neuropathic Pain

>50% pain reduction:

- Antidepressants 3.3
- Anticonvulsants 4.2
- Opioids 2.5

Finnerup et al. Pain 118:289-305;2005

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Study: Gilron et al. NEJM 2005

Patients: 57 patients, (DN=35; PHN=22)

Design: RCT, crossover, 4x5 weeks, target daily dose ceilings:

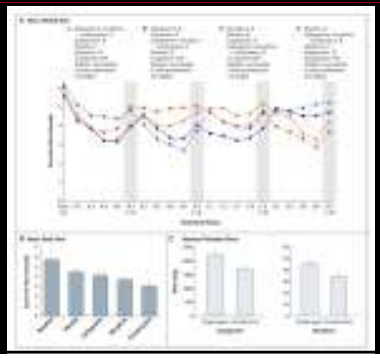
morphine 120mg

gabapentin 3200mg

morphine 60mg + gabapentine 2400mg

active placebo (lorazepam 1.6mg)

Morphine, Gabapentin, or Their Combination for Neuropathic Pain



Invasive procedures

Neuropathic Pain Treatment

Pain clinics

- Complicated patients handling
- Complex pharmacotherapy
- Invasive procedures

IV LIDOCAINE FOR NEUROPATHIC PAIN (Tremont-Lukats. Anesth Analg. 2005)

Study	Design	Diagnosis	n =	Outcome
Galer 1996	RCT, crossover	Nerve damage	23	+ (dose related)
Wallace 1996	Crossover	Nerve damage, Vs Pl	11	+ (dose related)
Medric 1999	RCT	LS radiculoparthy, Vs Am + Pl	30	L > Am
Rowbotham 1991	RCT	PHN, Vs MO + Pl	19	NS
Baranowsky 1999	RCT	PHN	24	NS
Attal 2000	RCT	Central pain	16	+ (> 50% pain ↓)
Finnerup 2005	RCT	Sp.cord disease	24	+ (> 36% than P, NNT)
Elleman 1989	RCT	Cancer-related NP	20	NS
Sjogren 1989	Crossover	Cancer-related NP	10	NS
Bruera 1992	Crossover	Cancer-related NP	10	NS
Kastrup 1987	RCT	PNP	15	+ (>50% responders)
Bakonja 1999	RCT	PNP	31	(dose related, 5-10 h)+
Attal 2004	RCT	Nerve damage+PHN	24	+ (> 50% pain ↓, more with MH)
Tremond-Lukats 2005	RCT	PNP	32	+ (> 30% pain ↓, > 50% responders)

IV LIDOCAINE META-ANALYSIS

(Tremont-Lukats. Anesth Analg 2005)

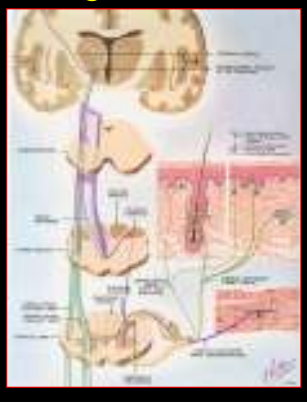
- 15 RCTs; 165 patients treated by a single lidocaine infusion and 164 by placebo
- Effective doses range: 1.5-5 mg/kg, equal to plasma concentration 0.6 - 5 µg/ml
- Continuous lidocaine infusion during 30-60 min is more effective than bolus dose
- Peak of pain relief varies from a few minutes to up to 40-60 minutes
- Post-infusion analgesic effect varies from 20-30 min to 2-4 weeks.
- **Mean reduction (VAS) = -10.02 (-16.51- - 3.45 mm, *p*=0.002)**

IV KETAMINE FOR NP EVIDENCE-BASED REVIEW

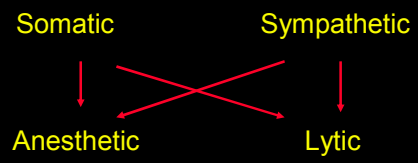
(Hocking. Anesth Analg.2003)

- Sub-anesthetic doses of ketamine may provide analgesic effect in NP. Ketamine is used mostly for severe acute episodes of refractory NP.
- Most studies showed efficacy at infusion doses of 0.125-0.5 mg/kg/hour during 4-6 hours or for several days
- > 50% pain relief was achieved only in some studies; other studies showed only up to 30% pain reduction, yet significantly more effective than placebo
- Most significant results were demonstrated in PHN and phantom pain

Ascending Pain Pathways

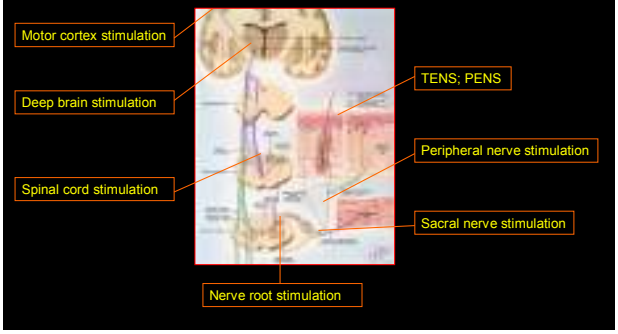


Nerve Blocks

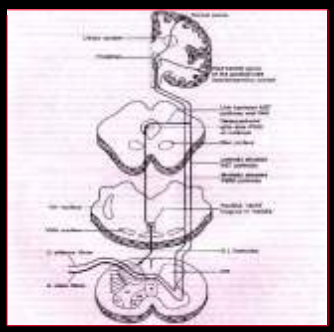


Post-Thoracotomy Pain Syndrome

Neural Stimulation for Pain Control



Descending Pain Pathways



Long-Term Peripheral Nerve Stimulation for Painful Nerve Injuries

Elon Eisenberg, Hannan Waisbrod,† and Hans U. Gerbershagen‡*

(Clin J Pain 2004;20:143–146)

TABLE 1. Nerves Selected for Stimulation (n = 46)

Lower Extremity		Upper Extremity/Head/Trunk	
Nerve	Patients	Nerve	Patients
Sciatic	10	Median	6
Femoral	10	Ulnar	4
Posterior tibial	4	Radial	2
Peroneal	4	Intercostal	3
LFCN	2	Greater occipital	1

LFCN, lateral femoral cutaneous nerve.

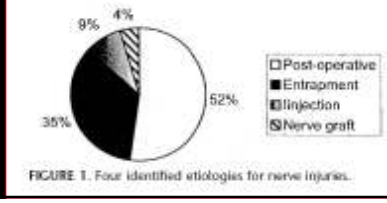


FIGURE 1. Four identified etiologies for nerve injuries.

TABLE 3. Results According to Etiologic Factors

Etiology	n	Results	
		Good	Poor
Operative trauma	24	20	4
Entrapment	16	14	2
Post injection	4	2	2
Post nerve-graft	2	0	2

Overall, pain intensity dropped from a VAS of 69 ±12 before surgery to 24 ± 28 at follow-up ($P < 0.001$).

Spinal Cord Stimulation

Electrode placement:

Spinal Cord Stimulation for Neuropathic Pain

"Good" indications:

- FBSS (lumbosacral >Cervical radiculopathy)
- CRPS
- Nerve injury
- Stump pain
- PHN with sensory sparing
- Incomplete spinal cord lesions
- Diabetic or other peripheral neuropathies

Spinal Cord Stimulation versus Repeated Lumbosacral Spine Surgery for Chronic Pain: A Randomized, Controlled Trial

North, Richard B. M.D.; Kidd, David H. M.A.; Farrokhi, Farrokh M.D.; Piantadosi, Steven A. M.D., Ph.D.

Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

Neurosurgry 2005;16:98-107

SCS versus Repeated Spine Surgery

Study design

- 50 patients with FBSS > 3 years postoperatively
- Scheduled for reoperation by standard criteria
- Randomized to SCS or reoperation
- Patients could crossover to the alternative
- Evaluation by independent third party
- Outcome: pain relief, patient satisfaction, use of analgesics, ADL and work status

North et al., Neurosurgry 2005;16:98-107

SCS versus Repeated Spine Surgery

Types of repeated operations

• Discectomy	11
• Laminectomy	42
• Foraminotomy	36
• Fusion	7
• Instrumentation	10
• Total	50

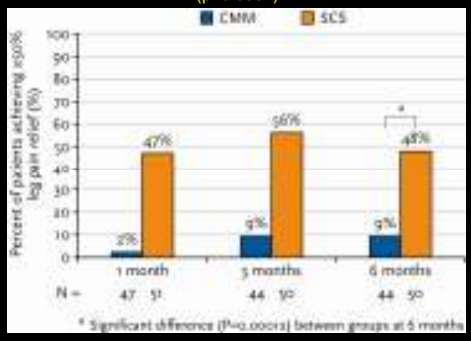
North et al., Neurosurgry 2005;16:98-107

SCS versus Repeated Spine Surgery

	SCS (n=24)	Reoperation (n=26)
2 year f/u	19	26
Crossover	5 (21%)	15 (54%)
Success (>50% pain relief, would you do it again?)	9 (47%) (43% of crossovers)	3 (12%) (0% of crossovers)
Opioid use increasd	3 (13%)	11 (42%)
ADL/work	No difference	

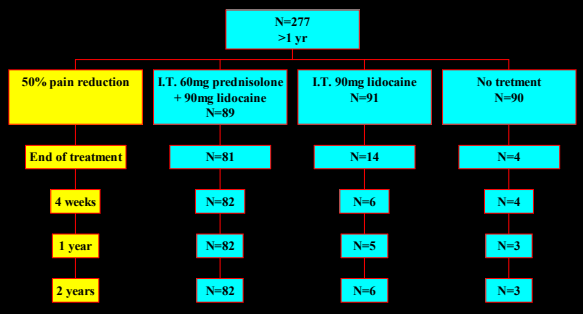
Primary outcome: ≥50% leg pain relief

Significantly more SCS patients (48% vs 9%) achieved the primary outcome (p=0.0001)



Treatment of Post-Herpetic Neuralgia

Intrathecal methylprednisolone study:



Kotani et al. N Engl J Med 2000;343:1514-9

Intrathecal Drug Delivery

- When everything else fails
- Opioids +/- local anesthetics
- Low dose (1/300 of oral morphine)
- High efficacy
- Relatively safe?

Nerve Injury – Surgical Interventions