Neuropathic Pain
Presentation, Mechanisms and Management

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Pain Matters, Liverpool
and The Alexandra Hospital, Cheadle, UK

Liverpool: European capital of culture 2008

Pain Relief Foundation
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Definition

- Definition of NPP
  "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"
  Neuropathic pain: Redefinition and a grading system for clinical and research purposes, Treede R-D T et al., Neurology 2008; 70(18):1630-1635

Neuropathic pain: classification

<table>
<thead>
<tr>
<th>Peripheral</th>
<th>Spinal</th>
<th>Brain</th>
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</thead>
<tbody>
<tr>
<td>post surgery</td>
<td>spinal injury</td>
<td>stroke</td>
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<tr>
<td>nerve injury</td>
<td>MS</td>
<td>MS</td>
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<td>plexus avulsions</td>
<td>tumour</td>
<td>tumour</td>
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<td>amputation</td>
<td>arachnoiditis</td>
<td>epilepsy</td>
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<td>compression syndr.</td>
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<td>herpes zoster</td>
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<tr>
<td>trig. neuralgia</td>
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<tr>
<td>neuropathies</td>
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Shingles and post herpetic neuralgia (PHN)

- Shingles
  - Dormant varicella zoster virus following chicken pox
  - Reactivated virus migrates from DRG along nerves to SC and skin
  - Painful blisters in the distribution of the nerve(s)
  - Blisters crust over and heal (4-6 weeks)
  - Estimated 300K – 1M cases / year in USA
- PHN
  - Pain continues or reappears post rash
    • (Study inclusion criterion - commonly states >3m duration)

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PHN – Pain character

- Character:
  - Burning, shooting, electric shocks, lancinating
  - Continuous or episodic
  - Spontaneous
  - Evoked (e.g. triggered by touch - clothing, breeze, temperature change)
  - Allodynia
    - Triggered by non-noxious stimulus
  - Numbness
  - Pruritus

PHN – Likelihood after shingles

- Overall frequency after 821 cases of shingles (Boston USA):
  - ~ 5% at 3 months, and 3% at one year
  - Age
    - < 50 years PHN 4.5% (at 60 days after onset)
    - ≥ 50 years > 20-fold higher prevalence
  - Few associations
    - Only prodromal sensory symptoms and compromised immunity increased the risk of progression to PHN

Histological changes in PHN

- Ganglia
  - Swelling and inflammation - primarily lymphocytic reaction
  - Neuronal loss
    - Degenerated ganglion cells and haemorrhagic necrosis
- Spinal cord, brain stem, meninges, root entry zones
  - Inflammation
- Peripheral nerves
  - Inflammation and focal demyelination
- In the months following infection:
  - Fibrosis in the ganglia, peripheral nerve, and nerve root
  - Degeneration occurs in the ipsilateral posterior column
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- 78 yr old widow
- HZ 3 years ago after death of husband
- Spontaneous burning pain
- Intermittant shooting pain- severe
- Marked allodynia: unable to tolerate clothes
- Marked distress and disability
- GP Rx Paracetamol and Codeine

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CRPS type I
- Continuous, diffuse limb pain, often burning in nature, and consequent on injury or noxious stimulation; associated and probably worsened by disuse
- Presents with various sensory, motor, and autonomic and trophic changes
- Not a true NPP, many different aetiologies? (see Baron)

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CRPS type II
- Exactly the same, except nerve injury has occurred (Mitchell)
- Causalgia, RSD
- Peripheral nerve injury, or cord or brain injury
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Hot or cold limb, persistent burning pain, allodynia, sweating abnormalities, reduced skin perfusion

Central pain
Damage to modulation of ascending pathways within brain or spinal cord (SC) traumatic or degenerative injury to spino-thalamic-cortical pathways
Not included: wind-up, plasticity, PHN, phantom pain, spasticity

Definition
• CNP arises from damage to ascending spino-thalamo-cortical pathways, their relays, or end-stations in the spinal cord or brain
• Usually a pain in an area of altered sensation
• More difficult to treat than peripheral NPP
Brain damage

- Central post-stroke pain, including vascular
- Multiple sclerosis, demyelination
- Cancer and treatment
- Epilepsy
- Parkinsons
- Wallenbergs degeneration
- Cluster?

Central post-stroke pain (CPSP)

- Described nearly 100 years ago
- Thalamic pain syndrome, most common
- Lesion of postero-lateral-ventricular nucleus
- Only 25% of these develop pain
- Other areas of damage also cause pain
- May arise at time, or develop up to 2 years later; classically described at 6 months
- Patient often discharged by this time
- May affect large areas or one specific area, e.g. hand or foot
- Can be affected by stress or physical ill-health, and reduced by alleviation of disorder, as with all NPP

Central post-stroke pain (CPSP) (2)

- In a population of 60,000,000, 100,000 strokes per year
- 35% mortality
- Approx 10% incidence (8%-16%)
- 5 to 10 thousand per year
- Approx 50,000 in population, or < 1 / 1000
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SCI
After ANY disturbance of SC
- Traumatic
- Degenerative
- Occurs in 65% of injuries
- 33%+ report severe pain
- Also known as myelopathic pain
- Pain can be proportional to injury
- Less with complete transection (hence cordectomy as treatment)

Levels of injury and extent of paralysis
- Cervical (neck)
- Thoracic (upper back)
- Lumbar (lower back)
- Sacral (back)
- Coccygeal (sacrum)

SCI traumatic
- USA - 11,000/YR (young)
- Total 500,000
- 78% Male (16-30)
- MVA (42%)
- Not all paralysed
- 1 in 500 of population
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SCI degenerative

- Polio
- Spina bifida
- Tumours
- M.S., demyelination
- Arachnoiditis
- Cordotomy, Drez
- Vascular
- Cauda equina syndrome
- Lead/mercury toxicity
- Radiation/chemo
- Myelitis
- AIDS (SIDA)
- B 12 deficiency

SCI (2)

- May also come some time after injury, or at time
- May be radicular at or even above level of injury, dermatomal, 2ndry to dorsal NR damage
- Segmental pain at or above level of sensory loss, often burning or shooting, and hyperalgesia, allodynia

Syringomyelia

- De Novo, or after SCI
- Can occur many years after injury (mean 6 years)
- Look for rising sensory loss
- Pain common - 60-80%
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Multiple sclerosis
- Up to one third develop pain
- 57.5% (Osterberg) of which 27.5% CNP
- 4.9% TGN
- 87% lower extremities
- 31% upper extremities
- 76% bilateral
- 88% daily pain
- 98% sensory abnormality
- Allodynia + hyperalgesia (Finnerup + Jensen)

Cancer
- Gonzales - Sloan Kettering
- 2 to 4% of patients hospitalised with cancer had CNP, primary or metastatic, therapy, surgery, radiation, chemo

Trigeminal neuralgia: diagnostic criteria
1. Paroxysmal attacks of facial pain, lasting a few seconds to less than two minutes
2. Characteristics (4 of 5)
   - Distribution along one or more trigeminal nerve divisions
   - Sudden, intense, sharp, superficial, stabbing or burning in quality
   - Severe in intensity
   - Precipitation from trigger areas, most by activities such as eating, talking, washing the face, or cleaning the teeth
   - Between paroxysms the patient is asymptomatic
3. No neurological deficit
4. Attacks are stereotyped in the individual patient
5. Exclusion of other causes of facial pain by history, physical examination and special investigations when necessary
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Epidemiology

- CPSP 1/1000
- SCI trauma 1/400
- Multiple other causes
- STOPNEP (Bouhassira) estimate 8% of population have NPP, 2% CNP
- So generally accepted to be found in 1% to 3% of population

Prevalence/incidence of neuropathic pain in different conditions

- 20–24% of diabetics experience PDN
- 25–50% of patients >50 years with herpes zoster develop PHN (3 months after healing of rash)
- 20% of women develop post-mastectomy pain
- One-third of cancer patients have neuropathic pain (alone or with nociceptive pain)
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Symptoms of neuropathic pain

- Spontaneous pain
  - Shooting, burning or electric shock-like
  - Numbness, pins and needles
- Allodynia
  - Pain in response to normally non-painful stimuli
- Hyperalgesia
  - Increased sensation of pain in response to normally painful stimuli

Dworkin RH et al., Arch Neurol 2003; 60:1524–1534

Allodynia

- Thermal
  - Heat
  - Cold
- Mechanical
  - Punctate
  - Dynamic

Diagnosing neuropathic pain

- Diagnosis is based on:
  - Medical history
  - Physical and neurological examination
  - Appropriate laboratory tests and investigations
  - Questionnaires
- e.g.
  - LANSS
  - DN4
  - PainDetect
  - Neuropathic Pain Q
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Quantitative sensory testing

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Altered sensation

- Many patients have an area of altered skin sensation, pain arising in this area
- Some have little or subtle change, not appreciated by physician
- Temp deficit important, assess with finger vs. metal
- Pinprick, with sharp stick vs. blunt stimulus

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GPs are pivotal in the management of neuropathic pain

- Most patients see their GP first
- Patients with neuropathic pain visit their GP frequently
- The majority of patients are ultimately managed by their GP
- Only a small proportion of all patients seen by GPs have neuropathic pain
- Recognising neuropathic pain in primary care can be challenging
- Enhanced education in pain is needed

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Allodynia (2)
- Pain from a stimulus not normally provoking pain, e.g. light touch or cold
- Mechanical: movement, stretching, touch, brushing
- Thermal: heat or cold
- Within but not throughout painful area
- Found in 70% of CPSP
- Various types should be recorded, e.g. brushing, cold, stretching
- Occurred elicited by stimulus outside painful area

Dysaesthesia
- An unpleasant abnormal sensation, whether spontaneous or evoked, below level of injury
- AKA Deafferentation pain, anaesthesia dolorosum
- Found after denervation
  - e.g. RF to Gasserian ganglion, cordotomy

Hyperalgesia
- An increased pain response to a stimulus which is normally painful
- cf. illness behavior
- Extreme sensitivity to pain
Paraesthesia

- An abnormal sensation, e.g. numbness, pins and needles, crawling ants etc., whether constant or evoked

Autonomic

- May be an element of SMP
- Limb may just be cold to touch, or feel cold, because of restricted use
- Consider Ca channel blocker, clonidine, Sympathetic Block (diagnostic first)

Mechanisms

- Transmitter or receptor depletion
- Adrenergic
- Gabergic
- Glycine
- Prostanoid
- Glutamate
- Na and Ca channels
- NMDA receptors
- Facilitatory pathways enhanced
- Inhibitory pathways diminished
- Central sensitisation
- Neuronal plasticity
- Genetic differences important
- Not correctable at present time
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Co-morbidity associated with peripheral neuropathic pain

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty sleeping</td>
<td>60</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>55</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>39</td>
</tr>
<tr>
<td>Concentration difficulties</td>
<td>36</td>
</tr>
<tr>
<td>Depression</td>
<td>33</td>
</tr>
<tr>
<td>Anxiety</td>
<td>27</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>18</td>
</tr>
</tbody>
</table>

% patients with moderate to very severe discomfort due to symptoms (n=126)

Meyer-Rosberg K et al., Eur J Pain 2001;5:379–389

Peripheral neuropathic pain drugs: NNT

- Tricyclic antidepressants
- Venlafaxine
- Amitriptyline
- Desipramine
- Nortriptyline
- Carbamazepine
- Valproate
- Gabapentin
- Pregabalin
- Methylphenidate
- Antidepressants (SNRI)
- Antidepressants (SSRI)
- Antidepressants, SNRI
- Antidepressants, SSRI
- NMDA antagonists
- Capsaicin
- Tramadol
- Oxycodone
- Opioids
- Topiramate

Finnerup N et al., Pain 2005;118:289–305
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Algorithm for neuropathic pain treatment: an evidence based proposal

Peripheral neuropathic pain

Lidocaine plaster

Postherpetic neuralgia and focal neuropathy

Yes

TCA

No

TCA contraindication

Gabapentin/Pregabalin

Yes

Tramadol, Oxycodone

TCA (SNRI)

Finnerup et al., Pain 2005;118:289–305

Dosage of TCAD's

- Start low – go slow
- Suggest Nortriptylene 10mg o.n.
- Weekly increase
- Artificial saliva/peardrops for dry mouth
- Constipation, drowsiness, dizziness, cardiac, etc.

Other antidepressants

- Venlafaxine 75 mg daily- to b.d.
- SSRI's for depressed patients
- Duloxetine
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Anticonvulsants

- Carbamazepine  (for TGN)
- Valproate  (fairly weak)
- Gabapentin  (lots of good trial work)
- Pregabalin  (latest- good trial work)
- Lamotrigine  (not great in practice)
- Phenytoin  (depressant effect)

Dosage for anticonvulsants

Again, start low go slow!

- Carbamazepine  100mg -1600mg
- Valproate  600mg – 1500mg
- Gabapentin  300mg – 6000mg+
- Pregabalin  50mg – 600mg
- Lamotrigine  25mg – 200mg

Cannabinoids

- Systematic review of cannabinoid derivatives tested in cancer, chronic non-malignant and post-operative pain
- Cannabinoids no more effective than codeine in controlling pain
- Adverse effects [e.g. CNS depression] limit their use

Concluded:
"Their (cannabinoids) widespread introduction into clinical practice for pain management is therefore undesirable"

Campbell F et al., Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative, systematic review. Bmj 2001;323:13–16
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Peripheral neuropathic pain drugs: NNH (withdrawal of Rx)

- Topiramate
- Tramadol
- Capsaicin
- NMDA antagonists
- Tricyclic antidepressants
- Antidepressants, SNRI
- Opioids
- Gabapentin/pregabalin
- Carbamazepine/levetiracetam/phenytoin
- Mast cell stabilizer
- Valproate
- Antidepressants, SSRI
- Lidocaine plaster

Finnerup et al., Pain 2005;118:289–305

Topicals
- Fentanyl
- Transtec
- BuTrans
- Lidoderm
- Capsaicin

NB importance of dose, position

Mode of action
I. Topical Lidocaine
   - Lidocaine diffuses into the skin
   - Stabilization of neuronal membranes
   - Down regulation of sodium channels
   - Pain reduction

epidermis
- dermis (neuronal level)
subcutaneous tissue (systemic level)
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Refactory patients with NPP
50% relief achieved by 35% of patients

Neuropathic pain: unmet needs

Blocks/Interventions

- Sympathetic blocks? (early only)
- SCS
- Intrathecal:
  - Baclofen for spasticity (+ve trial)
  - Clonidine
  - Opioids
  - Midazolam
  - Ziconitide
  - Morphine and clonidine (Siddall)
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Neural blockade
- Epidural steroids for sciatica
- Acute: good
- Chronic: reasonable, temporary (only with X-ray control)
- DRG's
- Acute zoster: steroid injections
- CRPS / SMP: sympathectomy, guanethidine

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Dorsal Root Ganglion

Advanced family
Synchromed II programmable pump

Spiral cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial
in patients with failed back surgery syndrome

Krisden Kumar 1, 2, Rod S. Taylor 3, Lisa Jacques 1, Sam Elshafie 4, Maria Miglio 1, Juan Molina 1, Steven Thonnard 5, Ian O’Cullogh 1, Elie Elnabhany 2, Jonathon Richardson 6, Richard W. North 1

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Pain 2001; 89: 81-90
Infusion and implants

- Opioids – 1 RCT for Ca pain, 1 review
- Buprenorphine
- Ziconitide
- Clonidine
- Ketamine
- Baclofen for spasticity
- LA yes, but how useful?
- Use of pumps dropping in USA - lack of evidence, side-effects, cost, complex dosing regimes hard to validate
- Pain Soc guidelines

Feeding sequence of cone snail

Photograph by Bruno Gaget

Neurosurgical

- Decompression DNP
- Neuroma
- Cordotomy (Ca, old work)
- DREZ SCI/avulsion
- Ablation of nerves
- Ganglionectomy
- Rhizotomy
- Midline myelotomy
- Deep brain stim.
- Motor cortex, better, less s.e.
- TGN decompression
- Carpal tunnel
HZ and PHN
(if primary management fails)

HZ
• Epidurals with LA +/- steroids
• Sympathetic blocks - both useful
• ? number/intervals to be used
• Not preventative of PHN

PHN
• IT steroids and LA - grade A but caveats
• Sympathetic - no evidence (?sub-groups)
• SCS "**" - 1st line
• IT DD (Deer, Zic) - 2nd line
• DBS, MCS - no specific data

Painful diabetic neuropathy
(if primary management fails)

• SCS (Tesfaye) "***"
• 7 yr fu (Daousi) benefit maintained
• Peripheral n. decompression
• ITDD

Radicular pain, sciatica, FBSS
(if primary management fails)

• Epidural steroids
• Acute: Good evidence
• Chronic: Reasonable, temporary
• Neck > back
• Only with X-ray control
• Transforaminal > intralaminar back (better)
• IL > TF neck (safer)
FBSS (mixed conditions with NPP)

- Physical therapy, exercise
- Drugs
- Psychological assessment, CBT
- Blocks, steroids
- SCS
- IDDS: Ziconitide, opioids
- MCS, DBS
- ReOp

CRPS

- Drugs
- Blocks level B, LA, sympathetic, early
- SCS
- ITDD Third line
- MCS / DBS
- Ablative SB poor evidence

Trigeminal neuralgia

- Meds, carbamazepine, oxcarbazepine
- MVD - younger patients in good health
- RF, glycerol, balloon - in older, ill, anxious
Percutaneous interventions

- **Radiofrequency thermocoagulation**
  - Sweet, 1965
- **Retrogasserian glycerol injection**
  - Hakanson, 1981
- **Balloon Compression**
  - Mullan Lichtor, 1983

SCI (3)

- Positive pregab, other meds
- Beware sedation- younger pts
- Coping skills
- Spinal cord stimulation
- Deep brain stimulation
- DREZ (in younger pts)

CPSP

- Start with tricyclics if no CI
- Add anticonvulsants and tramadol
- Consider opioid
- Start low, go slow with all dosages
- Cannabinoids

- Motor cortex stimulation - level C
- Deep brain stimulation
Summary

Neuropathic pain
- Types of neuropathic pain
- Mechanisms involved in neuropathic pain
- Types of patient that suffer from neuropathic pain
- Treatment, difficulties with treatment
- Although these patients are difficult to help, it is possible to help them

Thank you!