Painful Diabetic Neuropathy – Effective Management

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Neuropathic Pain

- Prevalence varies between 10 and 90% depending on classification
- Accounts for 50-75% of non-traumatic amputations
  - 1.7 fold increase in the risk of amputation; 12 fold, if there is deformity; 36 fold, if there is a history of previous ulceration
- Mortality rate approximates 25-50% within 5-10 years of diagnosis
Neuropathic Pain

- Neuropathic pain is also often associated with:
  - Sleep interference
  - Emotional disturbance
  - Reductions in quality of life and functioning
  - Reduced employment status
Symptoms of Neuropathic Pain

- **Spontaneous pain**
  - Shooting, burning or electric shock-like
  - Numbness, pins and needles

- **Hyperalgesia**
  - Increased sensation of pain in response to normally painful stimuli

- **Allodynia**
  - Pain in response to normally non-painful stimuli
Co-morbidity Associated with Peripheral Neuropathic Pain

- Difficulty sleeping: 60%
- Lack of energy: 55%
- Drowsiness: 39%
- Concentration difficulties: 36%
- Depression: 33%
- Anxiety: 27%
- Poor appetite: 18%

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

Mechanism of Damage

Tomlinson DR et al Nat Rev Neurosci 2008;9:31-35
Damaged Nerves

(A) Unmyelinated nerve fiber
(B) Damaged unmyelinated nerve fiber

Vesal nervorum
Myelinated nerve fiber
Occluded vesal nervorum
Damaged myelinated nerve fiber
Classification

- Subclinical neuropathy
  - Abnormalities in electro-diagnostic and quantitative sensory testing

- Diffuse clinical neuropathy
  - Distal symmetric sensorimotor and autonomic syndromes

- Focal syndromes
Subclinical Neuropathy

- Diagnosed by
  - Abnormal electro-diagnostic tests with decreased nerve conduction velocity or decreased amplitudes
  - Abnormal quantitative sensory tests for vibration, tactile, thermal thresholds
  - Autonomic function tests with diminished heart rate variation with deep breathing, Valsalva manoeuvre, and postural testing
Autonomic Neuropathy

25-year-old normal patient

25-year-old diabetic patient

Watkins PJ et al
Diffuse Peripheral Neuropathy

- Diabetes may damage small fibres, large fibres, or both
- These can lead to dysfunction of almost any segment of the somatic peripheral and autonomic nervous systems
- The size of the fibres involved often determines the order in which they are affected
Fibre Size and Symptoms

- Small fibres are affected earliest, manifested first in the lower limbs by pain and hyperalgesia

- Loss of thermal sensitivity follows, with reduced light touch and pinprick sensation

- Large fibre neuropathies may involve sensory or motor nerves, or both
Clinical Presentation of Large Fibre Neuropathy

- Presentation
  - Impaired vibration perception
  - Pain of A-type: deep-seated, gnawing
  - Ataxia
  - Wasting of small muscles, intrinsic minus feet with hammer toes
  - Weakness
  - Increased blood flow (the hot foot)
  - Risk of Charcot neuroarthropathy
However

- Most patients with distal sensory polyneuropathy have a mixed variety, with both large and small nerve fibre involvement.

- With a distal sensory polyneuropathy, a "glove and stocking" distribution of sensory loss is very common.
Different Presentations of Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Large fiber Neuropathy</th>
<th>Small fiber Neuropathy</th>
<th>Proximal motor Neuropathy</th>
<th>Acute mono Neuropathies</th>
<th>Pressure Palsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory loss: 0-+++</td>
<td>Sensory loss: 0-+</td>
<td>Sensory loss: 0-+</td>
<td>Sensory loss: 0-+</td>
<td>Sensory loss in Nerve distribution: +++++</td>
</tr>
<tr>
<td>(Touch, vibration)</td>
<td>(thermal, allodynia)</td>
<td>Pain: ++++</td>
<td>Pain: ++++</td>
<td>Pain: +++++</td>
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<tr>
<td>Pain: ++++</td>
<td></td>
<td>Tendon reflex: N↓</td>
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<td>Tendon reflex: N↓</td>
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<td>Tendon reflex: N↓↓↓↓</td>
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<td>Proximal Motor deficit: +++++</td>
<td>Motor deficit: +++++</td>
<td>Motor deficit: +++++</td>
</tr>
<tr>
<td>Motor deficit 0-+++</td>
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</tbody>
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Truncal

Medial popliteal

Ulnar

Lateral popliteal
Natural History

- Sensory and autonomic neuropathies are generally progressive and irreversible
  - Progression is related to glycaemic control

- Mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived and tend to recover
  - Recovery is dependent on restoration of good glycaemic control
Examples
Mononeuritis vs Entrapment

**Mononeuritis**
- Sudden onset
- Usually single nerve, but maybe more
- Common nerves C3, 6, 7, ulnar, peroneal
- Not progressive and resolves spontaneously
- Treatment symptomatic

**Entrapment**
- Gradual onset
- Single nerve exposed to trauma
- Common nerves: Median, ulnar, peroneal, medial and lateral plantar
- Progressive
- Treatment: rest, splints, diuretics, steroids, surgery
Proximal Motor Neuropathy

- Amyotrophy
  - Primarily affects the elderly
  - Gradual or abrupt onset
  - Begins with pain in the thighs and hips or buttocks
  - Followed by significant weakness of the proximal muscles of the lower limbs with inability to rise from the sitting position
  - Begins unilaterally and spreads bilaterally,
  - Coexists with distal symmetric polyneuropathy, and
  - Spontaneous muscle fasciculation, or provoked by percussion
Proximal Motor Neuropathy

- Secondary causes may be more common and not related to diabetes
  - Chronic inflammatory demyelinating polyneuropathy (CIDP),
  - Monoclonal gammopathy,
  - Circulating GM1 antibodies and
  - Antibodies to neuronal cells and inflammatory vasculitis
Proximal Motor Neuropathy

- Clinical features
  - Weakness of the iliopsoas, obturator, and adductor muscles, together with relative preservation of the gluteus maximus and minimus and hamstrings. Great difficulty rising out of chairs unaided and often use their arms to assist themselves
  - Heel or toe standing is preserved
Proximal Motor Neuropathy

- Treatment
  - Formerly thought to resolve spontaneously in 1.5 to 2 years, but now, if found to be immune-mediated, can resolve within days on immunotherapy
Distal Symmetric Polyneuropathy

A Simplified View of The PNS

Motor | Sensory | Autonomic
---|---|---
Myelinated | Myelinated | Thinly myelinated
Un-myelinated | Thinly myelinated | Un-myelinated

Aα | Aα/β | Aδ | C

Large | Small

Muscle control
Touch, Vibration, Position perception
Cold perception
Warm perception
Pain
Pain
Heart Rate, Blood Pressure, Sweating, GIT, GUT, function
Distal Symmetric Polyneuropathy

Distal Symmetric Diabetic Neuropathies Subtypes

- Large Fiber
  - Motor
  - Vibration
  - Position sense
  - Touch/pressure
  - Interferes with QOL and ADL

- Small Fiber
  - Pain
  - Autonomic
  - Thermal
  - Produces symptoms and leads to morbidity and mortality
Small Fibre Neuropathies

- Can be acute or chronic
- Pain (variable character) and parasthesiae
- May be disabling
- Can be difficult to treat
Large Fibre Neuropathies

- Impaired vibration perception (often the first objective evidence) and position sense
- Depressed tendon reflexes
- Aδ type deep-seated gnawing, dull, like a toothache in the bones of the feet, or even crushing or cramp-like pain
- Sensory ataxia (waddling gait)
- Wasting of small muscles of feet with hammertoes with weakness of hands and feet
- Shortening of the Achilles tendon with pes equinus
- Increased blood flow (hot foot)
Treatment

- Good glycaemic control underlies all treatments
- BP control is also important
- Increasing evidence that statins and ACE inhibitors help to prevent the progression of established disease
Treatment Aimed at Pathogenesis

- **Aldose reductase inhibitors**
  - inhibiting tissue accumulation of sorbitol and fructose
  - preventing reduction of redox potentials

- **Alpha-lipoic acid**
  - A thiol replenishing and redox modulating agent

- **Gamma-linolenic acid**
  - Important for preservation of nerve blood flow

- **Aminoguanidine**
  - An inhibitor of the formation of advanced glycosylation end products

- **IVIg**
Diabetic Neuropathy - NNT

- Tricyclics
- Duloxetine
- Venlafaxine
- Carbimazole
- Valproate
- Gabapentin
- Pregabalin
- Lamotrigine
- Topiramate
- Morphine
- Oxycodon
- Tramadol
- Aspirin in diethyl ether
- Topical lidocaine
- Topical capsaicin
- Cannabinoids

NNT for Diabetic Neuropathy to Receive 50% Pain Relief

NNT for Diabetic Neuropathy to Receive 50% Pain Relief

For Diabetes Neuropathy to
NNT for Post Herpetic Neuralgia to Receive 50% Pain Relief

Hempenstall et al Abstract 113 Pain Society meeting 2004
Very Recent Data

- A meta-analysis of pregabalin use in 7 trials
- 1,510 patients – 953 on the drug, 557 on placebo
- Pain assessed using a visual analogue scale

Conclusions

- Pain was relieved in a dose dependent manner
  - A >1 point reduction in pain was achieved in 60 days for those on placebo, 13 days for those on 150 mg/d, 5 days for those on 300 mg/d and 4 days for those on 600mg/d

Freeman et al Diabetes Care 2008;31(7):1448-1454
Neuropathy

- Ask annually about symptoms

- Be alert to the psychological consequences of chronic, painful diabetic neuropathy and offer psychological support according to their individual needs
Neuropathy

- Start with simple analgesia
- Then low dose tricyclics and titrate the dose up
- Then chose from duloxetine, gabapentin or pregabalin (which drug depends on price). Get to top dose, if one does not work, try another
- Try an opioid if anticonvulsants do not work

NICE Clinical Guideline 66 May 2008
Every year, formally ask about neuropathic symptoms

If present:
- discuss cause and prognosis
- agree appropriate therapeutic options and review understanding at each clinical contact
- be alert to psychological consequences and offer support appropriate to need

Uncontrolled
- Offer tricyclic drug, starting at low doses; titrate as tolerated
  - Discuss timing for most benefit
  - Advise that it is a trial of therapy

Uncontrolled
- Offer trial of cheapest (at maximum dose) of duloxetine, gabapentin or pregabalin
  - Stop if ineffective at maximally tolerated dose
  - Try another of the drugs if side effects limit dose titration

Uncontrolled
- Consider trial of opiate analgesia

Controlled
- Consider reducing dosage/stopping therapy following discussion and agreement with person concerned

Uncontrolled
- Discuss with the person and seek assistance of local chronic pain management team if agreeable

NICE CG 89 May 2009
Enquire annually for neuropathic symptoms (paraesthesia, burning sensations, shooting pains, other)

Assess severity if present
(sleep disturbance, depression, interference with normal activities)
Maintain good blood glucose control

Non-severe
Offer local measures and simple analgesia
Monitor for worsening

Controlled

Monitor for worsening or remission

Severe
Offer local measures and trial of tricyclic medication
Monitor for response

Controlled

Uncontrolled*

Add a trial of the cheapest (at maximum dose) of duloxetine, gabapentin, or pregabalin
– monitor for response

Controlled

Uncontrolled*

Consider a trial of another of duloxetine, gabapentin, or pregabalin – titrate dose and monitor for response

Controlled

Uncontrolled*

Monitor for worsening or remission

Review for opiate analgesia, pain clinical referral and psychological support
After the diagnosis of neuropathic pain and appropriate management of the underlying condition(s)

People with painful diabetic neuropathy

**First-line treatment**
- Offer oral duloxetine.
- Offer oral amitriptyline* if duloxetine is contraindicated.
- See box A for dosages.

Consider referring the person to a specialist pain service and/or a condition-specific service¹ at any stage, including at initial presentation and at the regular clinical reviews, if:
  - they have severe pain or
  - pain significantly limits their daily activities and participation² or
  - their underlying health condition has deteriorated.

Perform:
- early clinical review (see box B)
- regular clinical reviews (see box C).

Unsatisfactory pain reduction at maximum tolerated dose

Second-line treatment
- Offer treatment with another drug instead of or in combination with the original drug, after informed discussion with the person (see box A for dosages):
  - if first-line treatment was with duloxetine, switch to amitriptyline* or pregabalin, or combine with pregabalin
  - if first-line treatment was with amitriptyline¹, switch to or combine with pregabalin

Satisfactory pain reduction

Continue treatment – consider gradually reducing dose over time if improvement is sustained

Second-line treatment
- Offer treatment with another drug instead of or in combination with the original drug, after informed discussion with the person (see box A for dosages):
  - if first-line treatment was with amitriptyline¹ (or imipramine or nortriptyline¹), switch to or combine with pregabalin
  - if first-line treatment was with pregabalin, switch to or combine with amitriptyline¹ (or imipramine or nortriptyline¹) as an alternative if amitriptyline¹ is effective but the person cannot tolerate the adverse effects.

Perform:
- early clinical review (see box B)
- regular clinical reviews (see box C).

Unsatisfactory pain reduction at maximum tolerated dose

Third-line treatment
- Refer the person to a specialist pain service and/or a condition-specific service¹.
- While waiting for referral:
  - consider oral tramadol instead of or in combination² with second-line treatment (see box A for dosages)
  - consider topical lidocaine³ for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.

**Other treatments**
- Do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service¹.
- Other pharmacological treatments that are started by a specialist pain service or a condition-specific service¹ may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

NICE CG 96 March 2010
Any Questions?