Diabetic Painful Neuropathy

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Diabetic peripheral neuropathic pain (DPPN) is a disabling complication and presents a significant clinical challenge. Among those with diabetic neuropathy, it is estimated that up to a third (30%) develop painful symptoms.
Scale of the Challenge:

- Study of three urban general practice surgeries located in Liverpool, United Kingdom (UK) included 350 diabetic subjects

- Definition of DPPN
  Typical neuropathic pain symptoms in their legs for at least 1 year, Pain Symptom Score ≥ 3
  + Neuropathy Disability Score (NDS) of >6 OR
  NDS score ≥ 3 and Neuropathy Symptom Score (NSS) ≥ 5

- 16.2% of diabetes individuals had DPPN v 4.9% of general population (hospital treated cohort had slightly higher prevalence)\(^1\)

\(^1\) Dousi et al, Diabetic Medicine (2004)
Scale of the Challenge:

• In an observational study (n = 15,692) of diabetic patients receiving community-based care in North-West England:
  • Prevalence of painful symptoms (NSS ≥5) was 34% and DPPN (NSS ≥5 and NDS ≥3) was 21%.¹
  • DPPN was more prevalent in patients with type 2 diabetes (~2X), women, and people of South Asian origin.

¹Abbott et al, Diabetes Care (2011)
Diabetic peripheral neuropathic pain (DPPN) is a disabling complication and presents a significant clinical challenge.

Among those with diabetic neuropathy, it is estimated that up to a third (30%) develop painful symptoms.

Despite this, there is a lack of emphasis on neuropathic pain in diabetes centres nationwide.
Poor pain management is well recognised

- Almost 40% of the patients with diabetes and DPPN had never received any pharmacological treatment.\(^1\)
- 30% of the patients had been prescribed medication with no known efficacy in neuropathic pain, either in individual or combination regimes.
- 12%-30% have never talked about their pain with a physician.\(^2\)

\(^1\) Dousi et al, Diabetic Medicine (2004)  
\(^2\) Peltier et al BMJ 2014
Diabetic peripheral neuropathic pain (DPPN) is a disabling complication and presents a significant clinical challenge. Among those with diabetic neuropathy, it is estimated that up to a third (30%) develop painful symptoms. Despite this, there is a lack of emphasis on neuropathic pain in diabetes centres nationwide. Pain review, when undertaken, is usually during routine diabetes or foot clinic appointments, where the focus of management is directed elsewhere. In addition, primary care support, at times, is limited.
Neuropathic Pain: Definition

• Classical: ‘Pain caused by a lesion or disease of the somatosensory nervous system’
Clinical Features

- Onset: Gradual or insidious
- Symptoms usually start in the toes - progress proximally to feet and legs
- In more severe cases, there is upper limb involvement
- In more advanced disease - wasting of the small muscles of the hands and limb (legs and arms) weakness, become apparent.
Clinical Features

Typical neuropathic symptoms:

- Uncomfortable tingling (dysesthesia),
- Pain (burning; shooting or “electric-shock like”; lancinating or “knife-like”; “crawling”, or aching etc),
- Evoked pain (allodynia, hyperesthesia),
- Unusual sensations (severe coldness of the legs when clearly the lower limbs look and feel fine, odd sensations on walking likened to “walking on pebbles” or “walking on hot sand,” etc.)
Important points

Abbott study (2011)- 16000 pts

Pain scores are not affected by
- Severity of neuropathy
- Insulin use,
- Foot deformities,
- Smoking, or alcohol.

Women had 50% increased adjusted risk of painful symptoms compared with men (OR = 1.5).
## Mechanisms of Neuropathic Pain

<table>
<thead>
<tr>
<th>Peripheral Mechanisms</th>
<th>Central Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in sodium channel distribution and expression</td>
<td>A–β fibre sprouting into lamina II of the dorsal horn</td>
</tr>
<tr>
<td>Altered neuropeptide expression</td>
<td>Reduced Inhibition of descending Pathways</td>
</tr>
<tr>
<td>Peripheral sensitisation</td>
<td>Central sensitisation</td>
</tr>
<tr>
<td>Altered peripheral blood flow</td>
<td></td>
</tr>
<tr>
<td>Damage to small fibres</td>
<td></td>
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<tr>
<td>Glycaemic flux</td>
<td></td>
</tr>
</tbody>
</table>
Altered functional brain connectivity

Anterior cingulate cortex

Basal ganglia

Altered opioid levels in PAG

Increased excitatory and decreased inhibitory descending from RVM

- Central sensitization
- Microglial priming

Nociceptor

Sensitization, Sprouting, Priming

Microglia

DRG

Dorsal horn

TNERS
Examination findings

- Surprisingly few
- A lot hedges on the history
- Features of Diabetic Neuropathy may be present
- Many subjects, especially those with acute pain, may have no signs

- Remember: Small Fibre Neuropathy does not present with too many clinical signs
Which of these two pictures belongs to someone with DPPN?
Examination findings

- Surprisingly few
- A lot hedges on the history
- Features of Diabetic Neuropathy may be present
- Many subjects, especially those with acute pain, may have no signs

- Remember: Small Fibre Neuropathy does not present with too many clinical signs
Neuropathy is a Spectrum

No Neuropathy
Neuropathy is a Spectrum

No Neuropathy

Minimal neural slowing within normal limits
Neuropathy is a Spectrum

No Neuropathy

Minimal dysfunction within normal limits

Small fibre Neuropathy
Neuropathy is a Spectrum

No Neuropathy
- Minimal neural slowing within normal limits

Small fibre Neuropathy

Early Large Fibre Defects

- Light Touch
- Vibration
- Proprioception
Neuropathy is a Spectrum

- **No Neuropathy**
  - Minimal neural slowing within normal limits
- **Small fibre Neuropathy**
- **Early Large Fibre Defects**
- **Large fibre changes**

**Legend:**
- \( \alpha \) Axon to skin
- \( \beta \) Axon to muscle

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensory Receptors</th>
<th>Diameter (µm)</th>
<th>Speed (m/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Proprioceptors of skeletal muscle</td>
<td>12-20</td>
<td>70-170</td>
</tr>
<tr>
<td>II</td>
<td>Mechanoreceptors of skin</td>
<td>6-12</td>
<td>30-70</td>
</tr>
<tr>
<td>III</td>
<td>Pain, temperature</td>
<td>1-6</td>
<td>5-30</td>
</tr>
<tr>
<td>IV</td>
<td>Temp, pain, itch</td>
<td>0.2-1.5</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>
Neuropathy is a Spectrum

- No Neuropathy
  - Minimal neural slowing within normal limits
- Small fibre Neuropathy
- Early Large Fibre Defects
- Large fibre changes
- Loss of Protective Sensation
- Complete lack of sensation
Small Nerve Fibres

<table>
<thead>
<tr>
<th>1° Axon to skin</th>
<th>1° Axon to muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aα Group I</td>
<td>Aβ Group II</td>
</tr>
<tr>
<td>12-20 70-170</td>
<td>6-12 30-70</td>
</tr>
<tr>
<td>Proprioceptors of skeletal muscle</td>
<td>Mechanoreceptors of skin</td>
</tr>
<tr>
<td>Aδ Group III</td>
<td>C Group IV</td>
</tr>
<tr>
<td>1-6 5-30</td>
<td>0.2-1.5 0.5-2</td>
</tr>
<tr>
<td>Pain, temperature</td>
<td>Temp, pain, itch</td>
</tr>
</tbody>
</table>

Diameter (μm) Speed (m/sec)
## Differentials of Diabetic Neuropathic Pain

### Primary
- Idiopathic small fibre neuropathy
- Burning mouth syndrome
- Hereditary/genetic Na\(^{+}\)v1.7 mutations
- Na\(^{+}\)v1.8 mutations
- Familial amyloid polyneuropathy
- Fabry’s disease
- Tangier’s disease

### Secondary
- **Spinal Structural Disease**
  - Metabolic Impaired glucose tolerance
  - Rapid glycaemic control
  - Vitamin B12 deficiency
  - Dyslipidaemia
  - Hypothyroidism
- **Chronic kidney disease**
  - Infections
    - HIV
  - Hepatitis C
  - Influenza
  - Toxins and drugs
    - Anti-retrovirals
  - Antibiotics—metronidazole, nitrofurantoin, linezolid
  - Chemotherapy—bortezomib
  - Flecaïnide
  - 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
# Investigations (King’s protocol)

<table>
<thead>
<tr>
<th>Haematology</th>
<th>Biochemistry</th>
<th>Immunology</th>
<th>Neurophysiology</th>
<th>Radiology</th>
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<tbody>
<tr>
<td>FBC</td>
<td>UE</td>
<td>Immunoglobulins</td>
<td>NCS</td>
<td>MRI LS Spine</td>
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<tr>
<td>ESR</td>
<td>LFT</td>
<td>Protein electrophoresis</td>
<td>VPT</td>
<td></td>
</tr>
<tr>
<td>Coeliac screen</td>
<td>CRP</td>
<td>ANA</td>
<td>NDS</td>
<td></td>
</tr>
<tr>
<td>B12 Folate, Iron profile</td>
<td>ANCA</td>
<td>IENFD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone profile</td>
<td>Hepatitis Serology</td>
<td>CCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>HIV if appropriate</td>
<td>Microneurography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vit D</td>
<td>Antiphospholipid abs</td>
<td>Thermal Thresholds</td>
<td></td>
<td></td>
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<tr>
<td>TSH</td>
<td>Cryoglobulins</td>
<td></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>Vasculitis Panel</td>
<td></td>
<td></td>
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<tr>
<td>HbA1C</td>
<td>Paraneoplastic Abs (to discuss)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PSA (males)</td>
<td></td>
<td></td>
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</tr>
</tbody>
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### Assessment of the Severity

<table>
<thead>
<tr>
<th>Pain Questionnaire</th>
<th>QOL Questionnaire</th>
</tr>
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<tbody>
<tr>
<td>painDetect</td>
<td>NeuroQol</td>
</tr>
<tr>
<td>Likehart score</td>
<td>Norfolk Quality of Life Scale</td>
</tr>
<tr>
<td>McGill</td>
<td></td>
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<tr>
<td>BPI-MSF</td>
<td></td>
</tr>
</tbody>
</table>
Pain Severity Assessment

- No pain
- Moderate pain
- Unbearable pain

Scale from 0 to 10
Treatment

DPNP

Pharmacological

Topical
- Capsaicin
- Topical Nitrate
- Lignocaine Patch
- Opsite spray

Parenteral
- Tricyclic
- Selective Norad Reuptake inhibitors
- Sodium channel blockers
- Opioids Antiarrhythmic

Non Pharmacological

TENS, Acupuncture, Relaxation therapy
Pharmacological Treatment

Supra-spinal*
- CBZ
- GBP
- DLXT
- PGB

Spinal Cord*
- Ziconotide
- CBZ
- GBP
- PGB
- DLXT

Dorsal Root Ganglia*
- CBZ

Nerve Terminal
- Lidocaine
- Capsaicin

IronWood Labs 2013
Pharmacological Treatment

Painful diabetic neuropathy

Consideration of contraindications and comorbidities

- $\alpha_2$-$\delta$ agonist
  - (pregabalin or gabapentin)
- TCA
- SNRI
  - (duloxetine)

If pain control is inadequate and considering contraindications

- TCA or SNRI
- SNRI or $\alpha_2$-$\delta$ agonist
  - (pregabalin or gabapentin)
- TCA or $\alpha_2$-$\delta$ agonist
  - (pregabalin or gabapentin)

If pain control is still inadequate

Add opioid agonist as combination therapy

PDN = Peripheral diabetic neuropathy; SNRI = Serotonin-norepinephrine reuptake inhibitor; TCA = Tricyclic antidepressants.
Initial Management

Good glucose control

Ensure all other differential diagnosis are explored and treated

Pain Score <5

Topical Measures
Relaxation therapy
Ensure good footwear and foot gets adequate rest
Consider drug therapy (impaired sleep etc)

Pain Score >5

Topical Measures (may not work)
Early introduction of pain drugs
Relaxation therapy
Ensure good footwear and foot gets adequate rest
Topical Options

Lignocaine 5% Patch

Apply for 12 hours/day

May be cut into half
Topical Options

OPSITE spray

Cooling effect
Topical Options

Capsaicin Patch
Depletes Nociceptors
Not Licensed in UK
Drugs

Pregabalin
Start at 75mg OD
Max dose 600mg/day
Improves sleep
Anxiolytic
Drugs

Duloxetine

Start at 60 mg OD
Older people 30 mg

Mild antidepressant
Pain

- Poor sleep
- Anxious
- Renal failure

  → Pregabalin
  → Gabapentin

- Depressed
- Good Renal Function

  → Duloxetine
Numbers Needed to Treat

- BTX-A: 0.33
- TCAs: 579
- Opioids: 243
- Lidocaine patch: 797
- SNRIs: 333
- Tramadol: 389
- Gabapentin/pregabalin: 122
- Capsaicin: 431
- SSRIs: 214
- NGX capsaicin: ns
- Cannabinoids: ns

NNT
Effects of iv Lidocaine on Spontaneous Pain

**Responders’ profile = spontaneous pain and mechanical hyperalgesia**

Attal et al. *Neurology*, 2004
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin

Technology appraisal guidance [TA159]  Published date: 22 October 2008
In Research

Supplementation with thiamine, pyridoxine and cyanocobalamin
Benfothiamine in rat models as well as in human studies
Alpha-lipoic acid (ALADIN III Study, SYDNEY 2)
Pancreas Transplantation
Aldose Reductase Inhibitors (zani/ranirestat)
Trandalopril (Manchester group)
Combination Pain Therapy

Rationale - non-overlapping mechanism

Paucity of data
Polypharmacy, side effects
No data for central pain syndromes
Mean Daily Pain Baseline Score for Pain Intensity

Placebo  Gabapentin  Morphine  Combination

Mixed group including non diabetic patients

Gilron, NEJM, 2005
Drugs in Phase 2/3

NGF antibodies
- Tanezumab, Fulnarumab, REGN475
  - Phase II in DPN and Phase III in OA

Nav1.7 antagonists
- Xenon402, CNV1014802, PF-05089771

N-Type Ca++ channel blocker – Z160
  - Phase II low back pain / sacral radiculopathy (not in DPN)

Selective AT-2 Receptor antagonist – EMA401
  - Phase II in PHN (Lancet Feb 14) and chemotherapy-induced pain
Challenges in Pain Studies

- Despite advances in research and clinical trials, a considerable number of individuals do not get relief - NNT - 3-5 for most drugs
- Response is defined as a “30-50% reduction in pain severity
- Large powerful RCT’s lacking
- There is also the ‘placebo’ effect
- It is unclear which laboratory pain responses are most strongly associated with the experience of pain in daily life - R Edwards 2003 (Johns Hopkins)
King’s Neuropathic Pain clinic

Every 4th Wednesday PM

Upto 6 Patients

Ascertain diagnosis, exclude correctable factors

Targeted environment to discuss pain

Multiple aetiologies for pain—including psychological—needs time

Review in 1-2 months, initially but flexible, very like the DF model
Need for dedicated pain clinics in the management of diabetic painful peripheral neuropathy.

Prash Vas and Mike Edmonds
Referral Pathway

Pain in either foot in diabetes individual

Primary Care or Secondary care (including Main Diabetes clinic)

Referred through to Diabetes Foot clinic

Vascular and Biomechanical causes excluded

Referred to Specialist Neuropathic Pain clinic

Located within the Diabetes Foot Clinic
DPPN Clinic: Mission

1. Diagnostic confirmation of DPPN,
2. Exclusion of secondary causes, and
3. Ensure ongoing treatment maintenance.
Aim

To report our experience of undertaking a dedicated neuropathic pain clinic co-located within the diabetes foot unit clinic
Methods

- Patients attending a dedicated neuropathic pain clinic from April 2014 to August 2015.

Number referred (n=39)

- Vascular pathway, n=5
- Active ulcer and ulcer pain, n=1
- Acute Charcot, n=1
- Biomechanical pain n=1

DPPN pts seen, n=31

DFC gets 40-45 new referrals/month
Methods

• Patients attending a dedicated neuropathic pain clinic from April 2014 to August 2015.

• At baseline, investigations were carried out to rule out secondary causes of neuropathic pain.

• Pain management was undertaken according to NICE guideline CG173 (and also Toronto Consensus 2011 on DPPN). Patients reviewed every 2-3 months.
Painful diabetic peripheral neuropathy

Figure 1. Treatment algorithm for painful diabetic peripheral neuropathy

PDN = Peripheral diabetic neuropathy; SNRI = Serotonin-norepinephrine reuptake inhibitor; TCA = Tricyclic antidepressants.
# Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67±13</td>
</tr>
<tr>
<td>Male gender</td>
<td>65%</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>11.5±7.3</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White European</td>
<td>61%</td>
</tr>
<tr>
<td>South Asian</td>
<td>7%</td>
</tr>
<tr>
<td>African Caribbean</td>
<td>32%</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td>7%</td>
</tr>
<tr>
<td>OHA + newer</td>
<td>58%</td>
</tr>
<tr>
<td>Insulin + (OHA/Newer)</td>
<td>35%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>14%</td>
</tr>
<tr>
<td>EFGR&lt;30</td>
<td>20%</td>
</tr>
<tr>
<td>Impaired vision</td>
<td>14%</td>
</tr>
</tbody>
</table>
## Patient Characteristics

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical neuropathy</td>
<td>87%</td>
</tr>
<tr>
<td>Neuropathy Disability Score (NDS)</td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>7%</td>
</tr>
<tr>
<td>3-5</td>
<td>54%</td>
</tr>
<tr>
<td>6-7</td>
<td>16%</td>
</tr>
<tr>
<td>≥ 8</td>
<td>23%</td>
</tr>
<tr>
<td>Vibration Perception Threshold</td>
<td>27±11</td>
</tr>
<tr>
<td>Foot deformities</td>
<td>32%</td>
</tr>
<tr>
<td>Peripheral arterial disease (abnormal waveforms or mild arterial duplex changes)**</td>
<td>32%**</td>
</tr>
<tr>
<td>Foot ulcer history</td>
<td>3%</td>
</tr>
<tr>
<td>Active Ulcer</td>
<td>0%</td>
</tr>
<tr>
<td>Lower-limb amputation history</td>
<td>0%</td>
</tr>
</tbody>
</table>
Outcome:

31 patients were seen 115 times.

- Duration of classical painful symptoms $2.7 \pm 1.4$ years
- Baseline 11 point visual analogue score (VAS) was $7.5 \pm 1.6$.
- Only 32% (10/31) of patients were on current neuropathic pain medications at point of referral. Gabapentin (4), Pregabalin (2), Duloxetine (2), Valproate (1), Amitriptyline (1)

- 50% of the remainder (11/21) had been trialled on a ‘pain medication’ but had stopped it. Lack of efficacy and side effects were two main reasons offered.
At 6 months:

- At 6 months, VAS was 4.8±1.3
At 6 months

- At 6 months, VAS was 4.8±1.3
- Approximately
  - 50% of the patients improved their VAS by ≥3,
  - 25% by 1-2 points, and,
  - 25% did not show any improvement (ANOVA p<0.001 for trend).
- Overall, 22% halved their VAS scores at 6 months.
- Orthotics referrals were made for 5 patients. Further podiatry advice, engagement with community foot teams was provided as necessary.
Presence of additional painful comorbidity (DPPN+)

Figure 2. Coexistent Comorbidities in our cohort:
Conclusion

• Hospital referrals for management of DPPN are
  • Elderly,
  • Have had pain for a significant duration, and
  • Usually untreated at point of referral to hospital despite significant pain scores.

• 30% referred have painful comorbidities in addition, management of which *may* help improve pain scores.

• A pain clinic co-located within the diabetic foot clinic has the potential to deliver high quality and focused pain relief care.
Thank You

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