Management of Diabetic Peripheral Neuropathic Pain (DPNP)

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Acronyms and Abbreviations

• 5-HT = serotonin
• ACR = American College of Rheumatology
• AE = adverse event
• ALKPHOS = alkaline phosphatase
• ALT = alanine transaminase
• AST = aspartate transaminase
• BDI-II = beck depression inventory-II
• BID = twice daily
• BP = blood pressure
• BPI = brief pain inventory
• CGI-S = clinical global impressions of severity
• CHF = congestive heart failure
• CI = confidence interval
• CNS = central nervous system
• DC = discontinuation
• DLX = duloxetine
• DM = diabetes mellitus
• DPN = diabetic peripheral neuropathy
• DPNP = diabetic peripheral neuropathic pain
• EQ-5D = EuroQol-5 dimensions
• HbA1C = hemoglobin A1c
• HDL-C = high-density lipoprotein cholesterol
• LDL-C = low-density lipoprotein cholesterol
• LOCF = last observation carried forward analysis
• LS = least square
• MDD = major depressive disorder
• Mi = myocardial infarction
• MMRM = mixed-effects models repeated measures
• MNSI = Michigan Neuropathy Screening Instrument
• NE = norepinephrine
• NMDA = N-methyl-D-aspartate
• NSAID = nonsteroidal anti-inflammatory drug
• PBO = placebo
• PGI-I = patient global impression of improvement
• PNS = peripheral nervous system
• QD = once daily
• QoL = quality of life
• SAE = serious adverse event
• SF-36 = 36-item short-form health survey
• SF-MPQ = short-form McGill pain questionnaire
• SNRI = serotonin norepinephrine reuptake inhibitor
• TBILI = total bilirubin
• TCAs = tricyclic antidepressants
• TEAE = treatment-emergent adverse event
Diabetes and Diabetic Peripheral Neuropathy: Disease State and Incidence

• Presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes

1. Common and progressive complication of diabetes
2. Result of multiple metabolic insults to neurons and blood vessels
3. Associated with significant morbidity, including pain

• incidence

1. An estimated 171 million people in the world have diabetes
2. About 50% of people with diabetes develop some degree of neuropathy, including peripheral neuropathy

Epidemiology

• Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes
• PDN is frequently unreported 12.5% and more frequently untreated 39%
Diabetic Peripheral Neuropathic Pain: A Frequent and Debilitating Complication

- About 10-20% of patients with diabetic peripheral neuropathy develop pain
  - This pain broadly interferes with daily functioning and quality of life

1. General activity
2. Walking
3. Energy level
4. Social and leisure activities
5. Ability to sleep
6. Change in mood, feelings of depression and anxiety
7. Overall enjoyment of life

Classification of Diabetic Neuropathy

- **Mononeuropathy**: involvement of a single nerve characteristically results in foot drop, wrist drop, or cranial nerve III, IV, or VI paralysis
- **Radiculopathy**: a sensory syndrome of pain over multiple spinal nerves, mimics zoster pain
- **Diabetic amyotrophy**: a rare disorder resulting in atrophy and weakness of the pelvic girdle musculature
Classification of Diabetic Neuropathy

• **Autonomic neuropathy**: involvement of the involuntary nervous system. Can involve:
  - The gastrointestinal tract: gastroparesis, constipation, diarrhea
  - The cardiovascular system: orthostatic hypotension, tachycardia, alteration of heart rate control
  - The genitourinary system: impotence, urinary retention, incontinence
  - Other: abnormality in perspiration, excessive sweating or dryness
Classification of Diabetic Neuropathy

• **Peripheral sensorimotor polyneuropathy:** the most common of the diabetic neuropathies accounting for 80% of neuropathy in diabetic patients.
Signs and symptoms of Peripheral Sensorimotor Polyneuropathy

Distal, bilateral, symmetrical, stocking-glove distribution.

Symptoms range from numbness ("deadness") to severe pain. Burning, alteration of temperature sensation, parathesias, shooting, or stabbing pains are common.

May worsen at night.

Minor motor involvement causing weakness.
Physical Exam Clues to the Diagnosis

- Decrease or absent reflexes (Achilles)
- Loss or diminished vibratory sensation (128Hz tuning fork), pin prick, light touch, or pressure perception
- Muscle atrophy
- Foot complications, ulcerations, blisters, deformities (Charcot’s joint)
Figure 1. The ‘at risk’ diabetic foot (illustration by G. Kogler)
Electrophysiologic Studies

• Most sensitive, reliable, and reproducible measurement of nerve function which correlate with findings on biopsy

• NCV demonstrate demyelination and axonal degeneration in the form of decreased amplitudes of the compound muscle action potential and sensory action potential.

• The earliest finding is distal slowing of conduction with preservation of proximal NCV.

• EMG reveals denervation and reinnervation
Differential Diagnosis

Up to 10% have other etiologies

- **Metabolic etiologies**: B12/ folate deficiency, hypothyroidism, uremia
- **Toxic etiologies**: ETOH, heavy metals, medications
- **Inflammatory etiologies**: vasculitis, sarcoid, SLE, syphilis, leprosy
- **Other**: paraneoplastic, leukemia, amyloid
Hypothesized Pathophysiology of DN

- Polyol pathway
- Advanced glycation end products (AGE)
- Oxidative stress
Polyol pathway

• Hyperglycemia causes saturation of the normal glycolytic pathway in the nerves.
• Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase.
Polyol pathway

• Accumulation of sorbitol and fructose lead to:
  – reduced nerve myoinositol
  – decreased membrane Na+/K+ -ATPase activity
  – impaired axonal transport
  – structural breakdown of nerves
  – causing abnormal action potential propagation.

• The rationale for the use of aldose reductase inhibitors to improve nerve conduction
Advanced glycation end products (AGE)

• The non-enzymatic reaction of excess glucose with proteins, nucleotides, and lipids results in advance glycation end products that may have a role in disrupting neuronal integrity and repair mechanisms through interference with nerve cell metabolism and axonal transport.
Oxidative stress

- Production of free radicals - not fully understood.
- Direct damage to blood vessels leading to nerve ischemia and facilitation of AGE reactions.
- Use of the antioxidant alpha lipoic acid may hold promise
Related contributing factors

- Altered gene expression with altered cellular phenotypes
- Changes in cell physiology relating to endoskeletal structure or cellular transport
- Reduction in neurotropins
- Nerve ischemia
Pathophysiology

- Not clearly understood
- Polyol theory:

- Glycosolated end-products theory

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*Figure 1.* The Aldose Reductase Pathway of Glucose Metabolism. The aldose reductase pathway is activated by intracellular hyperglycemia, resulting in increased sorbitol formation. This, in turn (through an unknown mechanism, indicated by the question mark), results in decreased myo-inositol formation and ultimately decreased cellular activity of Na⁺/K⁺-ATPase. Hyperglycemia also directly inhibits ATPase activity (Ref. 5). The vertical arrows indicate increases (up arrow) and decreases (down arrow) in the substances in question.

*Figure 2.* Formation of Advanced Glycosylation End Products from Glucose. The formation of advanced glycosylation end products from glucose occurs through the nonenzymatic formation of early glycosylation products (N-glucosylamine) that then undergo acid-base catalysis to form Amadori products (1-amino-1-deoxy-ketose). Advanced glycosylation end products result from the degradation of the Amadori products into reactive carbonyl compounds that react with free amino groups (R-NH₂ in Ref. 6). The formation of advanced glycosylation end products in vivo is retarded by reductase (Ref. 6).
Role of Serotonin and Norepinephrine in Neuropathic Pain

- Pain perception Ascending nociceptive pathways\(^1\)
- Descending modulatory pathways\(^2\)

- Neuropathic pain associated with increased excitation and decreased inhibition of pain pathways
- Serotonin (5-HT) and norepinephrine (NE) are key modulatory neurotransmitters in descending inhibitory pathways\(^2,3\)
- Potentiation of 5-HT and NE activity in the CNS is believed to result in pain inhibition\(^2,3\)


- Cortex
- Lateral hypothalamus
- Thalamus
- Amygdala
- Medulla \(\supset\) Ascending nociceptive pathways
- Descending modulatory pathways - 5-HT +/- - NE -

- Interneuron\(^+\) = facilitates the perception of pain, \(-\) = inhibits the perception of pain
Modulation of pain via the descending pathways

• Brain send signal to the spinal cord to modulate pain
• Serotonin (5-HT) and norepinephrine play a role in descending pathway
• Modulation of pain starts in the prefrontal cortex (deals with thinking, attention, awareness and emotion)
• Limbic system which deals with stress and emotion also modulate pain
• Midbrain (nucleus raphe magnus and locus ceruleus) also modulate pain
Modulation of pain

• Pain signals arriving from the periphery stimulate release of endogenous opioids e.g. endorphins and enkephalins

• Endogenous opioids bind to opioids receptors in the ascending and descending pathway and brain to reduce pain

• After enkephalins binds to opioids receptors they stimulate the release of GABA that inhibit pain transmission in the spinal cord
Distinguishing Nociceptive and Neuropathic Pain

**Nociceptive pain**
- Identifiable stimuli that normally produce tissue damage
- Usually self-limiting or chronic due to inflammation
- Transmitted by structurally and functionally intact pathways
- Examples: post-operative pain, burns, ischemic pain

**Neuropathic pain**
- Often spontaneous (occurring without identifiable stimuli)
- Often chronic
- May involve structural and functional changes in pathways
- Examples: polyneuropathy (eg, diabetic, HIV), trigeminal neuralgia, central post-stroke pain.
*Figure 2. Patients with NIDDM and Control Subjects with Definite or Probable Polyneuropathy at Base Line and after 10 Years. P = 0.057 for the comparison between the groups at base line; at 10 years, P ≤ 0.001 -- both by the chi-square test.*
*Figure 1.-Prevalence of Clinical Symptoms and Signs in Patients with NIDDM and Control Subjects at Base Line and after 10 Years. Panel A shows the proportion of patients with bilateral pain in the legs and feet. Panel B shows the proportion with bilateral paresthesias of the legs and feet. Panel C shows the proportion with no Achilles-tendon reflexes, and Panel D the proportion with loss of vibration sensation on the medial malleoli. The comparisons of the groups at base line have been previously reported (Ref. 2). P values for the comparisons between patients and controls were derived with McNemar's test.*
# Diabetic Vascular Complication

<table>
<thead>
<tr>
<th>Microvascular Complications</th>
<th>Macrovascular Complications</th>
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<tbody>
<tr>
<td>• Diabetic Retinopathy</td>
<td>• Stroke</td>
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<tr>
<td>• Diabetic Nephropathy</td>
<td>• Heart diseases</td>
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<tr>
<td>• Diabetic Neuropathy</td>
<td>• Peripheral vascular diseases</td>
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Clinical Polyneuropathy
Clinical Polyneuropathy

• **Small-Fiber Neuropathy**
  Sensory loss: 0→+
  (thermal, allodynia)
  Pain: + →+++
  Tendon reflex: N→↓
  Motor deficit: 0

• **Large-Fiber Neuropathy**
  Sensory loss: 0→+++ (touch, vibration)
  Pain: + →+++ 
  Tendon reflex: N→↓↓↓
  Motor deficit: 0 →+++ 

• **Proximal Motor Neuropathy**
  Sensory loss: 0→+
  Pain: + →+++ 
  Tendon reflex: ↓↓
  Proximal motor deficit: 
  + →+++ 

• **Acute Mononeuropathies**
  Sensory loss: 0→+
  Pain: + →+++ 
  Tendon reflex: N
  Motor deficit: +→+++ 

• **Pressure Palsies**
  Sensory loss in nerve distribution: +→+++ 
  Pain: + →++ 
  Tendon reflex: N
  Motor deficit: +→+++ 

Diabetic Peripheral Neuropathy Disease State: Clinical Manifestations

• Subclinical Clinical

• DPN is a progressive disease starting with diminished nerve conduction velocity and ending with amputation

• Symptoms occur in approximately 25% of patients and may occur anytime and intermittently
What Defines QOL?

• WHO definition of QOL
• “An individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns”1
• Multidimensional assessment, which includes capacity to engage in activities, pursue interests, and internal well being2

Efficacy Measures: BPI


- The BPI is a scale that measures the severity of pain and the interference of pain with function. Severity and interference ratings range from 0 (no pain/does not interfere) to 10 (pain as bad as can imagine/completely interferes).

- Patients rate pain severity for worst pain, least pain, and average pain in past 24 hours; severity is also rated for the pain right now.

- Seven questions assess interference of pain in the past 24 hours for, general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

(no pain) 0 1 2 3 4 5 6 7 8 9 10 (worst pain)
Efficacy Measures: PGI-Improvement

- The PGI-Improvement is a patient-rated rating that evaluates change in how a patient feels in general since beginning treatment.
- Ratings range from 1 (very much better) to 7 (very much worse).
  - Mark the box that best describes how you (the patient) have felt in general since you started taking this medication.
- 1 Very much better
- 2 Much better
- 3 A little better
- 4 The same
- 5 A little worse
- 6 Much worse
- 7 Very much worse
Goals of Neuropathic Pain Treatment

• Primary goal – reduction in pain

• Secondary goals
  1. Improvement in physical function
  2. Reduction in affective distress
  3. Improvement in QoL
  4. Maintenance of positive outcomes
  5. Education of patient and providers

• Achieving these goals depends upon
  1. Accurate diagnosis of any underlying etiology
  2. Preventive treatment of underlying etiology (eg, diabetes and joint inflammation) if possible

Management

• Prevention of neuropathy through tight glycemic control, goal is to achieve “normal” levels

• Control of neuropathic pain
  – Simple analgesics (acetaminophen, NSAIDS)
  – Tricyclic antidepressants
  – SSRIs
  – Anticonvulsants
  – Mexilitine
  – Tramadol
  – Capsaicin

• Prevention of foot complications
Clinical Management of DPNP

• Pharmacologic treatments
  1. Serotonin norepinephrine reuptake inhibitors (duloxetine – approved)
  2. α2δ ligands (pregabalin – approved)
  3. Tricyclic antidepressants (eg, amitriptyline)
  4. Opioid analgesics (e.g., tramadol)
  5. Topical agents (e.g., lidocaine)

• ♦Nonpharmacologic treatments (eg, acupuncture and spinal stimulation)
Pharmacological Treatment Options of Neuropathic Pain

Peripheral sensitization

- **Na+ Channel Modulators**: Carbamazepine, Oxcarbazepine, TCAs, Topiramate, Lamotrigine, Lidocaine

- **Descending Inhibitory Pathways (NE/5-HT, enkephalins)**
  - TCA
  - SNRI SSRI
  - α-adrenergic blocking agents
  - Opioids
  - Tramadol
  - Cannabinoids

Central Sensitization

- **Ca2+ Channel Modulators**: Gabapentin, Levetiracetam, Oxcarbazepine, Lamotrigine, Pregabalin

- **NMDA antagonists**:
  - Ketamine
  - Dextromethorphan
  - Methadone
  - Memantine

- **Duloxetine**
National Institute for Health and Clinical Excellence (NICE): 2010 Guidelines

• Recommended Duloxetine as the only First-line Treatment for Painful Diabetic Neuropathy.
• **Duloxetine**: First-line Treatment for Painful Diabetic Neuropathy
• If duloxetine contraindicated, physicians can offer oamitriptyline, but an informed consent should be obtained/documented, since it is not indicated for PDN
• Physicians can offer oral amitriptyline or pregabalin as first-line treatment for neuropathic pain conditions in general, but for Painful Diabetic Neuropathy, it is recommended to offer duloxetine in particular.

• ♦The Guideline Development Group of NICE (GDG) agreed there is high-to-moderate-quality evidence for the efficacy of duloxetine
European Federation of Neurological Societies Task Force 2009 Treatment Guidelines for DPNP

• Recommendations for first-line treatment:
  – Duloxetine
  – Gabapentin
  – Pregabalin
  – TCA
  – Venlafaxine ER

• Recommendations for 2\textsuperscript{nd}/3\textsuperscript{rd} Line
  – Opioids
  – Tramadol

Possible Future Therapies

• **Aldose reductase inhibitors:**
  – inhibit aldose reductase, the rate limiting step in the formation of sorbitol in the polyol pathway
  – used in some countries for many years
Possible Future Therapies

• **Nerve Growth Factors:**
  – Apfel et al. Published first RCT in 1998
  – 250 pts, subcutaneous recombinant human nerve growth factor 3xweek for 6 months
  – Significant improvement in three endpoints
    • the sensory component of the neurological exam
    • two quantitative sensory tests
    • subjects impression of improvement
  – NGFs may be effective, current studies ongoing
Non-pharmacologic Modalites of Treatment

- Infrared therapy
- Shoe magnets
- Exercise
- Acupuncture
- External stimulation - transcutaneous electrical nerve stimulation
- Spinal cord stimulation
- Biofeedback and behavioral therapy
- Surgical decompression
- Intrathecal baclofen
Summary

• Diabetic neuropathy is common
  – up to 40-50% over a 10-25 year span
• The DCCT proved tight control can prevent neuropathy by 57-69% at 5yrs
• Once a patient develops neuropathy, there are few treatments proven to be effective
• Foot care is essential in preventing neuropathic complications
Asante Sana