Challenges with Diabetes Complications

Neuropathy

Daniel Bessesen, MD
Professor of Medicine
University of Colorado, School of Medicine
Chief or Endocrinology, Denver Health Medical Center
Daniel.bessesen@ucdenver.edu
Why Should we Care About Neuropathy?

• Decreased functional capacity and quality of life
• Risk for injury leading to ulceration amputation
• Increased direct and indirect health care costs
• Autonomic neuropathy
  • Falls
  • Erratic glucose control
  • Quality of life

Diabetes Care 36:3131–3138, 2013
Age-Adjusted Hospital Discharge Rates for Nontraumatic Lower Extremity Amputation (LEA) per 1,000 Diabetic Population, by Level of Amputation, United States, 1993-2009

Topics

• Types of neuropathy
• Screening and diagnosing
• Role of glucose control and other factors
• Treatment
Types of Neuropathy

• Distal Symmetric Polyneuropathy (DPN)
• Diabetic Autonomic Neuropathy: Cardiac, GI, GU,
• Mononeuritis
• Lumbosacaral radiculoplexopathy: Diabetic Amyotrophy

Diagnosing Diabetic Neuropathy

• Physical exam: touch, vibration, muscle mass, reflexes, pulse, orthostatics,
• Monofilament: 10 g
• Michigan Neuropathy Screening Instrument and others
• New methods
  – MR imaging
  – Skin biopsy
  – Corneal confocal microscopy
  – Sudoscan (electrochemical skin conductance)
MR T2 findings of Diabetic Neuropathy

With nerve death, there is increased T2 signal in nerve. May be useful in differentiating from compressive neuropathy.

AJR 2012; 199:407–412
Intra-Epidermal Nerve Fiber Density

Normal

Pre-Diabetes

Diabetes Care 29:1294–1299, 2006
Corneal Confocal Microscopy

Figure 1 — CCM showing the SNP. A: Normal SNP appearance in a healthy subject. B: CNF loss in a patient with recently diagnosed T2D. A single image frame with the commonly used size of 400 µm x 400 µm is displayed for comparison.

Diabetes 2014;63:2454–2463
Factors Associated with Neuropathy: Eurodiab Study

Odds ratios (95% CI)

- Hypertension: 1.57
- Smoking: 1.38
- HbA1c: 1.48
- Change in HbA1c: 1.36
- Diabetes duration: 1.40
- BMI: 1.27
- Triglycerides: 1.21
- Total cholesterol: 1.15

N = 1101 with type 1 diabetes mellitus; follow-up: 7.3 ± 0.6 years

Current Diabetes Reports 2009, 9:432–434
Treatments Based on Mechanisms:
(Not Much Here)

### Table 2—Treatment of diabetic neuropathy based on the putative pathogenetic mechanisms

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Compound</th>
<th>Aim of treatment</th>
<th>Status of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyol pathway ↑</td>
<td>Aldose reductase inhibitors</td>
<td>Nerve sorbitol ↓</td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Sorbinil</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Tolrestat</td>
<td></td>
<td>Ineffective</td>
</tr>
<tr>
<td></td>
<td>Ponalrestat</td>
<td></td>
<td>Withdrawn (marginal effects)</td>
</tr>
<tr>
<td></td>
<td>Zopolrestat</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Zenarestat</td>
<td></td>
<td>Withdrawn (AE)</td>
</tr>
<tr>
<td></td>
<td>Lidorestat</td>
<td></td>
<td>Effective in RCTs, trials ongoing</td>
</tr>
<tr>
<td></td>
<td>Fidarestat</td>
<td></td>
<td>Effective in RCTs, trials ongoing</td>
</tr>
<tr>
<td></td>
<td>AS-3201</td>
<td></td>
<td>Marketed in Japan</td>
</tr>
<tr>
<td></td>
<td>Epalrestat</td>
<td></td>
<td>Equivocal</td>
</tr>
<tr>
<td>Myo-inositol ↓</td>
<td>Myo-inositol</td>
<td>Nerve myo-inositol ↑</td>
<td>Effective in RCTs, trials ongoing</td>
</tr>
<tr>
<td>Oxidative stress ↑</td>
<td>α-Lipoic acid</td>
<td>Oxygen free radicals ↓</td>
<td>Effective in RCTs, trials ongoing</td>
</tr>
<tr>
<td>Nerve hypoxia ↑</td>
<td>Vasodilators</td>
<td>NBF ↑</td>
<td>RCTs ongoing</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td>Effective in one RCT</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin analogs</td>
<td></td>
<td>Effective in one RCT</td>
</tr>
<tr>
<td></td>
<td>phVEGF165 gene transfer</td>
<td></td>
<td>RCTs ongoing</td>
</tr>
<tr>
<td>Protein kinase C ↑</td>
<td>Protein kinase C-β inhibitor (ruboxistaurin)</td>
<td>Angiogenesis ↑</td>
<td>Studies ongoing</td>
</tr>
<tr>
<td>C-peptide ↓</td>
<td>C-peptide</td>
<td>NBF ↑</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Neurotrophism ↓</td>
<td>Nerve growth factor (NGF)</td>
<td>Nerve regeneration, growth ↑</td>
<td>Ineffective</td>
</tr>
<tr>
<td></td>
<td>BDNF</td>
<td>Nerve regeneration, growth ↑</td>
<td>Ineffective</td>
</tr>
<tr>
<td>LCFA metabolism ↓</td>
<td>Acetyl-l-carnitine</td>
<td>LCFA accumulation ↓</td>
<td>Ineffective</td>
</tr>
<tr>
<td>GLA synthesis ↓</td>
<td>γ-Linolenic acid (GLA)</td>
<td>EFA metabolism ↑</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>NEG ↑</td>
<td>Aminoguanidine</td>
<td>AGE accumulation ↓</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

AE, adverse event; AGE: advanced glycation end product; BDNF, brain-derived neurotrophic factor; EFA: essential fatty acid; LCFA, long-chain fatty acid; NBF, nerve blood flow; NEG, nonenzymatic glycation; RCT, randomized clinical trial.

Diabetes Care 2005 28, 956–962
Glucose Control and Neuropathy in Type 1 Diabetes

1441 pts initially randomized. 23 years later EDIC trial, 30% risk reduction from prior intensive treatment.

Glucose Control and Progression of Neuropathy: Type 2 Diabetes

FIGURE 1  Effect of intensive glycemic control on prevalence of peripheral neuropathy. There were no significant differences between treatment arms, either at baseline or at 24 months (STD, standard treatment arm. INT, intensive treatment arm).


VA Cooperative Trial
Glucose Control and Progression of Neuropathy: Type 2 Diabetes

Accord Trial: 10,251 patients randomized to intensive control (<6%) vs standard care (7-7.9%)
Treatment of Neuropathic Pain

- **Anticonvulsants:** Pregabalin, Gabapentin, Valproate, Carbamazepine, Topiramate,
- **Tricyclics:** Amitriptyline, Imipramine
- **SSRIs:** Duloxetine, Paroxetine, Venlafaxine, Citalopram
- **Topical analgesics:** Capsaicin, Mexiletine, Lidocaine
- **Analgesic Opiates:** Tramadol, Oxycodone
- **OTC medications:** \(\alpha\)-lipoic acid, carnitine
Treatment of Neuropathic Pain: Do the Studies Help?

- Heterogenous study designs
  - Different patient groups
  - Different approaches to measuring pain and relief
- Almost no head-to-head comparisons
- Commercial interest, publication bias
- New versus old medications
## Treatment of Neuropathic Pain

### Meta-analyses of drug therapy vs placebo for diabetic neuropathic pain

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Subjects (N)</th>
<th>Duration (wk)</th>
<th>Mean age (y)</th>
<th>Measured outcome</th>
<th>NNT (95% CI)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various tricyclic antidepressants and doses</td>
<td>177</td>
<td>3-12</td>
<td>50</td>
<td>Overall effectiveness</td>
<td>1.3 (1.2-1.5)</td>
<td>Treatment cessation: 28 (17.6-68.9)</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60 mg/d</td>
<td>655</td>
<td>12</td>
<td>N/A</td>
<td>50% pain reduction</td>
<td>6.0 (5-10)</td>
</tr>
<tr>
<td>120 mg/d</td>
<td>655</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>600 mg/d</td>
<td>1425</td>
<td>5-13</td>
<td>59</td>
<td>50% pain reduction</td>
<td>5 (4-6.6)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200-3600 mg/d</td>
<td>829</td>
<td>4-12</td>
<td>58</td>
<td>50% pain reduction</td>
<td>5.8 (4.3-9.0)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20-80 mg/d</td>
<td>36</td>
<td>4</td>
<td>63</td>
<td>Moderate pain relief (defined as a score of 3 on a 6-point scale)</td>
<td>2.6 (N/A)</td>
</tr>
</tbody>
</table>

*J Fam Pract. 2012 Nov;61(11):691-3: Summary of Cochrane Reviews*
Treatment of Neuropathic Pain: meta analysis

Pain Practice 14(2), 2014 167–184
Treatment of Neuropathic Pain: ADA

Other Causes: Compressive neuropathy, B12 Deficiency,


- Symptomatic neuropathy
  - Exclude nondiabetic etiologies
  - Stabilize glycemic control
    (insulin not always required in type 2 diabetes)
    - Tricyclic drugs
      (e.g., Amitriptyline 25–150 mg before bed)
      - Anticonvulsants
        (e.g., Gabapentin, typical dose 1.8 g/day)
        - Opioid or opioid-like drug
          (e.g., Tramadol, Oxycodone)
          - Consider pain clinic referral
# Treatment of Neuropathic Pain: AAN

<table>
<thead>
<tr>
<th>Level</th>
<th>Recommended drug and dose</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pregabalin, 300-600 mg/d</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td>B</td>
<td>Gabapentin, 900-3,600 mg/d</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate, 500-1,200 mg/d</td>
<td>Lacosamide</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine, 75-225 mg/d</td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Duloxetine, 60-120 mg/d</td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline, 25-100 mg/d</td>
<td>Mexiletine</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan, 400 mg/d</td>
<td>Magnetic field treatment</td>
</tr>
<tr>
<td></td>
<td>Morphine sulphate, titrated to 120 mg/d</td>
<td>Low-intensity laser therapy</td>
</tr>
<tr>
<td></td>
<td>Tramadol, 210 mg/d</td>
<td>Reiki therapy</td>
</tr>
<tr>
<td></td>
<td>Oxycodone, mean 37 mg/d, max 120 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsaicin, 0.075% QID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isosorbide dinitrate spray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electrical stimulation, percutaneous nerve stimulation x 3-4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

*Neurology 2011;76;1758-1765: American Academy of Neurology*
Treatment of Neuropathic Pain

Fig 2 | Algorithm for the treatment of painful diabetic neuropathy including first and second line treatments. SNRI = serotonin norepinephrine reuptake inhibitor

BMJ 2014;348:g1799
Summary

- Neuropathy is a common complication of diabetes that causes substantial disability.
- Be aware of and rule out other causes.
- The number of treatment options is increasing but the approach to treatment remains unsatisfactory.