Medications for the Treatment of Neuropathic Pain

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Jinny Tavee, MD
Associate Professor
Neurological Institute
Cleveland Clinic Foundation

Neuropathic Pain

- Pain, paresthesias, and sensory changes in region of neurological dysfunction
- May be related to ion channel dysfunction
- Examples:
  - Peripheral Neuropathy
  - Chronic radiculopathy
  - Trigeminal Neuralgia
  - Complex regional pain syndrome
  - Post herpetic neuralgia
  - Lower Back pain
  - Nerve trauma
  - Spinal cord injury pain
Pain is a localized form of sorrow

When there is pain, there are no words. All pain is the same.

Baruch Spinoza

Toni Morrison

Chronic Pain Guidelines

- Find and treat the underlying disorder
- First line medications: Non-opioids
- Second line medications: Opioids
- Interventional therapies
- Counseling
- Wellness measures: nutrition, exercise, and mind-body therapies
Principles of Treatment

• Goal: 30% reduction in pain or ≥2 on VAS

• Start low, go slow

• One drug at a time

• If combination therapy: choose meds with different mechanisms of action

Case

• 48 y/o man with longstanding DM II presents with 8 month history of progressively worsening painful neuropathy

• Severe numbness and burning paresthesias with itching sensations in his feet

• Worse at night and affects sleep
### First line: Antidepressants

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Dosages (per day)</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptiline</td>
<td>20-150 mg</td>
<td>Sedation, weight gain, anticholinergic effects, sexual dysfunction (side effects most prominent in amitryptiline)</td>
</tr>
<tr>
<td>Nortryptiline</td>
<td>20-150 mg</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>20-200 mg</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120 mg</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-225 mg</td>
<td>Anxiety, insomnia, weight loss, anticholinergic effects, sexual dysfunction, arrhythmia</td>
</tr>
</tbody>
</table>

*Depression and suicide risk with antiepileptics*
## Other Anticonvulsants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>25-400 mg</td>
<td>Weight loss, sedation, cognitive slowing, renal stones, paresthesias</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>500-3000mg</td>
<td>Dizziness, sedation, irritability</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25-400 mg</td>
<td>Stevens-Johnson's syndrome, rash, dizziness, nausea, sedation</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200-1200 mg</td>
<td>Dizziness, sedation, ataxia, aplastic anemia, liver enzyme elevation</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600-2400 mg</td>
<td>Dizziness, nausea, fatigue, leukopenia</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100-600mg</td>
<td>Weight loss, sedation, cognitive slowing, renal stones</td>
</tr>
</tbody>
</table>

## Non-opioids: Topical agents

### Topical anesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Route of Administration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 5%</td>
<td>3 patches</td>
<td>12 hrs</td>
<td>Local edema, burning, erythema</td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>0.025-.25%</td>
<td>TID-QID</td>
<td>Burning, worse with heat exposure</td>
</tr>
<tr>
<td>Capsaicin 8%</td>
<td>Apply 60-90 minutes</td>
<td>Burning, worse with heat exposure</td>
<td></td>
</tr>
</tbody>
</table>
Non-opioids on the horizon

• Lacosamide (Vimpat)
  – Anticonvulsant 100-600mg/D in divided doses
  – Reduces pain in diabetic neuropathy
  – HA, dizziness, cognitive changes, sedation, tremor

• Rufinamide (Banzel)
  – Anticonvulsant for Lennox Gastaut
  – 400-3200mg/D in divided doses
  – Phase II trials for neuropathic pain


Second line: Opioids

<table>
<thead>
<tr>
<th>Opioids/Opioid agonist</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>50-400mg in divided doses (q 4-6hrs)</td>
<td>Sedation, dizziness, seizures, nausea, constipation</td>
</tr>
<tr>
<td>Tapapentadol (Nucynta)</td>
<td>50-600mg in divided doses (q 4-6hrs)</td>
<td>Potential for addiction/abuse, sedation, constipation, nausea, sz</td>
</tr>
</tbody>
</table>

• May be effective short term (average 5 weeks duration)
• No evidence for maintained pain relief for longer periods of time
Opioids - Concerns

• Risk of abuse, addiction, dependency

• Loss of analgesic efficacy
  – Tolerance
  – Opioid induced hyperalgesia

• Risk of overdose
  – 9 fold increased risk of fatal OD when morphine equivalent dose (MED) > 100mg/D compared to 20mg/D
  – For each fatal OD, 7 nonfatal overdoses
  – Most are unintentional and occur in the home

• Litigation

• Respiratory depression, seizures

Franklin, AANEM 2010;Plenary:41-44

Morphine Equivalent Dosing

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose (mg) Parenteral</th>
<th>Dose (mg) Oral</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>3-4</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>3-4</td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
<td>3-4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>--</td>
<td>20-30</td>
<td>3-4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>30</td>
<td>3-4</td>
</tr>
<tr>
<td>Methadone</td>
<td>1-2</td>
<td>1-2</td>
<td>6-8</td>
</tr>
</tbody>
</table>
| Fentanyl patch  | 0.1                  | 17ug/h         | 48-72

Backonja, Neur Continuum 2009;5:64-100
Opioid Guidelines

• One prescribing physician
• One pharmacy
• Comprehensive risk evaluation
• Written opioid contract/agreement with patient prior to initiation
• Do not escalate dose if tolerance is suspected
  — substantial increase in dose with no substantial increase in pain relief

Franklin, AANEM 2010; Plenary: 41–44

Natural supplements: Alpha-lipoic acid

• Natural cofactor of dehydrogenase complex
• Ameliorated symptoms in diabetic neuropathy
  — IV 600mg/D in patients with DM distal sensory and autonomic neuropathy (14 treatments)
• Oral dose and length of treatment not well established
• Anecdotal side effects

Ziegler et al., Diabetes Care 1999; 22: 1296–301
Natural supplements: Acetyl-L-Carnitine

• **Chemotherapy PN**: Oral 1gm TID for 8 weeks in 25 patients with PN due to paclitaxel or cisplatin (Bianchi et al, 2003)
  – improved sensory neuropathy symptoms in 60% pts
  – Improved motor neuropathy in 92% of pts

• **Antiretroviral PN**: Oral 2gm/D for 4 weeks in 20 HIV+ pts with antiretroviral PN (Osio 2006)
  – Mean pain intensity score was significantly reduced
  – No change on EMG

• **Diabetes PN**: Oral 500 and 1000 mg TID for 6 and 12 months in 1335 patients with diabetic PN (Sima et al, 2005)
  – 27% with pain, all significantly improved in 1000mg TID group

Bianchi et al. Eur J Cancer 2005;41:1746-50;

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Back to the case

• A) Amitryptiline nightly, titrated up to 75mg/D
• B) Gabapentin TID titrated up to 3600mg/D
• C) Topiramate nightly, titrated up to 100mg/D
• D) Lidoderm patch under socks
• E) Acetyl-L-Carnitine 1000mg TID
• F) Tramadol 50-100mg/D for severe breakthrough
Cleveland Clinic

Every life deserves world class care.