Objective

Identify appropriate pharmacologic options for the treatment of neuropathic pain
Pain Signaling Overview

Inflammatory mediators sensitize nociceptors:
- Bradykinins
- Prostaglandins
- Substance P

Injury

Pain

Na+ and Ca++ Channels

Afferent nerves:
- A-Beta: myelinated, fast transmission
- A-Delta: myelinated, nociceptive stimuli (instantaneous pain)
- C-fibers: intense nociceptive stimuli (dull, achy pain)

NMDA (ascending, pro-pain)

5-HT, NE, GABA (descending, anti-pain)
Neuropathic Etiologies

Alcohol dependence
  › Concentration gradient damage similar to DM
  › Vitamin deficiency (thiamine, B12)

Chemotherapy
Painful diabetic neuropathy (PDN)
Fibromyalgia (FM)
HIV/AIDS
Nerve compression
Nutritional deficiency
  › E.g. thiamine, niacin, folic acid

Toxins
  › E.g. arsenic, lead, mercury, organophosphates

Pain Ther. 207;6(1):S35-42.
Antidepressants
Evidence for Use: Tricyclic Antidepressants

Most studied class in neuropathic pain

- PDN primary model in studies
  - Cochrane Review: 46 trials of TCAs in NP
  - Showed significant pain score improvement with TCAs vs. placebo
  - Comparative evidence between the TCAs
    - No significant differences found in trials
  - TCAs have been studied against: tramadol, capsaicin, fluphenazine, and venlafaxine
    - Amitriptyline > tramadol, capsaicin, fluphenazine

Cochrane Lib. 2007;Issue 4
Tolerability: TCAs

- Anticholinergic effects
  - Dry mouth
  - Increased fall risk
  - Delirium risk
- Orthostasis
- QTc prolongation
- Sedation
- Weight gain
- Mortality risk in overdose
### Evidence for Use: Venlafaxine

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowbotham et al.</td>
<td>Venlafaxine XR (75 mg OR 150 to 225 mg)</td>
<td>Double-blind</td>
<td>VAS Scores:</td>
</tr>
<tr>
<td>2004</td>
<td>Placebo</td>
<td>6 weeks</td>
<td>- 75 mg: reduced 32%</td>
</tr>
<tr>
<td>244 patients</td>
<td></td>
<td></td>
<td>- 150 to 225 mg: reduced 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Placebo: reduced 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- p&lt;0.001</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>Venlafaxine XR 225 mg</td>
<td>Double-blind</td>
<td>11-point Likert Scale:</td>
</tr>
<tr>
<td>2003</td>
<td>Imipramine 150 mg</td>
<td>Crossover</td>
<td>- Baseline: 7 points</td>
</tr>
<tr>
<td>40 patients</td>
<td></td>
<td>12 weeks</td>
<td>- 12 week:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Venlafaxine 5 points</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Imipramine 5.3 points</td>
</tr>
</tbody>
</table>

VAS: visual analog scale
Evidence for Use: Duloxetine

Duloxetine vs Placebo in Patients with Painful Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline Score (SD)</th>
<th>12-Week Score (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=115</td>
<td>5.8 (1.5)</td>
<td>3.89 (0.22)</td>
<td>NS</td>
</tr>
<tr>
<td>20 mg/day N=115</td>
<td>5.9 (1.6)</td>
<td>3.54 (0.21)</td>
<td>NS</td>
</tr>
<tr>
<td>60 mg/day N=113</td>
<td>6.0 (1.7)</td>
<td>3.11 (0.22)</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td>120 mg/day N=114</td>
<td>5.9 (1.4)</td>
<td>2.66 (0.23)</td>
<td>≤ 0.001</td>
</tr>
</tbody>
</table>
Evidence for Use: Duloxetine

Patients achieving > 50% reduction in pain:

- Placebo = 29 (26%)
- Duloxetine 20 mg/day = 46 (41%) \( (p<0.05) \)
- Duloxetine 60 mg/day = 55 (49%) \( (p<0.05) \)
- Duloxetine 120 mg/day = 57 (52%) \( (p<0.05) \)

Safety measures:

- No significant difference in lab values or BP
- Somnolence, nausea, constipation, and dizziness were more frequent in 120 mg/day group
- Constipation and somnolence more frequent in 60 mg/day group vs. placebo

Antidepressant Summary

- **TCAs:**
  - Most studied
  - Limited by tolerability
  - Potential prescriber discomfort

- **Venlafaxine:**
  - Target doses with norepinephrine activity (≥150 mg)
  - Comparable to imipramine

- **Duloxetine:**
  - Target doses ≥60 mg
  - Dose related adverse events
Anticonvulsants
Mechanism: Gabapentin & Pregabalin

Ca++ channel *modulator*

↓ Calcium influx
↓ Glutamate release
↓ Excitatory signal transmission
↓ Pain (hopefully)
## Evidence for Use: Pregabalin

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline Score (SD)</th>
<th>Endpoint Score (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6/6 (1.5)</td>
<td>5.06 (0.21)</td>
<td>NS</td>
</tr>
<tr>
<td>N=97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin 75 mg/day</td>
<td>6.7 (1.3)</td>
<td>4.91 (0.24)</td>
<td>0.626</td>
</tr>
<tr>
<td>N=77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin 300 mg/day</td>
<td>6.2 (1.4)</td>
<td>3.8 (0.23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>N=81</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin 600 mg/day</td>
<td>6.2 (1.5)</td>
<td>3.6 (0.23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>N=82</td>
<td></td>
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</tbody>
</table>

*Neurology. 2004;63:2104-2110*
Summarized Results: Pregabalin

Patients receiving >30% reduction in pain:
- Placebo: 33%
- Pregabalin 300 mg/day: 62%
- Pregabalin 600 mg/day: 65%

Patients receiving >50% reduction in pain:
- Placebo: 18%
- Pregabalin 300 mg/day: 46%
- Pregabalin 600 mg/day: 48%

Safety:
- Dizziness, somnolence and peripheral edema more frequent in 600 mg/day group vs. placebo
- Dizziness and somnolence more frequent in patients treated with 300 mg/day vs. placebo
Lamotrigine for Neuropathy

Na+ channel blocker → inhibits glutamate release

Cochrane Review (2013)

› 12 RCTs included (n = 1511 patients)
› Lamotrigine 200 – 400 mg/day vs. placebo
› No difference in benefit vs. placebo [HIGH quality of evidence]
› ~10% patients developed rash (NNH 27)

Carbamazepine for Neuropathy

Na+ channel blocker

Cochrane Review (2014)

- 10 RCTs (n = 480 patients)
  - Trigeminal neuralgia, PDN, post-stroke neuropathy (FM NOT included)
- CBZ 100 – 2400 mg/day vs. placebo or active
- CBZ provided superior pain relief (>50% reduction) vs. placebo (NNT 2) [LOW quality of evidence]
- ~27% patients had side effects (NNH 3)

Cochrane Lib. 2014;4.
Tramadol

Tramadol ➔ M1 via CYP2D6 & CYP3A4
   › μ-opioid receptor agonism: M1 ➔ tramadol
   › 5-HT & NE reuptake inhibition: tramadol ➔ M1

Drug interactions
   › CYP2D6 & 3A4 INHIBITORS ↓ analgesia
   › Potential for serotonin toxicity

Seizure risk
   › Most common in first ~10 days of therapy and in overdose scenarios

Cochrane Lib. 2006;3.
Opioids for Neuropathy

Falling out of favor for **chronic** neuropathy
› Recent pain guidelines emphasize psychological interventions and non-opioid Rx therapies
› Risk vs. benefit on case-by-case basis

**Cochrane Review (2013)**
› 14 RCTs (n = 845 patients) of duration < 12 weeks
› Short-term benefit observed (NNT = 6 to achieve >50% pain relief)
› No significant benefit in functioning observed

Cochrane Lib. 2013;8.
Conclusions
## Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Class/Agent</th>
<th>NNT (&gt;50% pain reduction)</th>
<th>NNH (drop out due to side effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>3.6</td>
<td>13.4</td>
</tr>
<tr>
<td>SNRIs</td>
<td>6.4</td>
<td>11.8</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>7.2</td>
<td>25.6</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>7.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Strong Opioids</td>
<td>4.3</td>
<td>11.7</td>
</tr>
</tbody>
</table>

N = 229 RCTs

# International Association for Study of Pain (NeuPSIG)

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Medication</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>TCAs</td>
<td>STRONG</td>
</tr>
<tr>
<td></td>
<td>SNRI</td>
<td>STRONG</td>
</tr>
<tr>
<td></td>
<td>Pregabalin/gabapentin</td>
<td>STRONG</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
<td>Tramadol</td>
<td>WEAK</td>
</tr>
<tr>
<td></td>
<td>Lidocaine topical</td>
<td>WEAK</td>
</tr>
<tr>
<td></td>
<td>Capsaicin topical</td>
<td>WEAK</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Line</td>
<td>Botox SC injection</td>
<td>WEAK</td>
</tr>
<tr>
<td></td>
<td>Strong opioids</td>
<td>WEAK</td>
</tr>
<tr>
<td>Don’t Use</td>
<td>Lamotrigine</td>
<td>STRONG</td>
</tr>
<tr>
<td></td>
<td>Cannabinoids</td>
<td>WEAK</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>WEAK</td>
</tr>
</tbody>
</table>

## NICE 2017 Guidelines

<table>
<thead>
<tr>
<th>Place in Therapy</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td></td>
<td>Duloxetine</td>
</tr>
<tr>
<td></td>
<td>Pregabalin/Gabapentin</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Tramadol– short term</td>
</tr>
<tr>
<td></td>
<td>Capsaicin cream*</td>
</tr>
<tr>
<td>Do Not Use</td>
<td>Cannabis</td>
</tr>
<tr>
<td></td>
<td>Lacosamide</td>
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<tr>
<td></td>
<td>Lamotrigine</td>
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<tr>
<td></td>
<td>Levetiracteam</td>
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<td></td>
<td>Opioids</td>
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<tr>
<td></td>
<td>Tramadol- long term</td>
</tr>
<tr>
<td></td>
<td><strong>Venlafaxine</strong></td>
</tr>
</tbody>
</table>
Assessment Question

Which of the following pharmacologic options is NOT a potential first line recommendations for neuropathic pain?

A) Gabapentin
B) Tramadol
C) Venlafaxine
D) Amitriptyline
Assessment Question

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A) Gabapentin
B) Tramadol
C) Venlafaxine
D) Amitriptyline
References